Mastering temptation: Behavioral, neural and physiological investigations of self-control in goal-directed choice

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Abstract

Self-control is a key skill that has important implications for life success. Parallel research programs in psychology, economics, and most recently neuroeconomics have identified important correlates and outcomes of self-control. Among those are for example educational achievements, financial stability, and health. However, the cognitive mechanisms underlying self-control remain elusive.

The influence of situational modulators of self-control capacity such as stress has been recognized, but behavioral observations show that the impact of such modulators varies widely between individuals. In order to better understand inter-individual differences in reactions to self-control challenges and the impact of situational modulators on the effective use of self-control, I investigated it at the neural level. Combining behavioral and neural levels of analysis may allow us to better detect and understand changes in cognitive mechanisms that explain when and why some individuals fail in using self-control when experiencing such states.

This thesis investigates the neural mechanisms underlying self-control in goal-directed choice using dietary self-control as a model behavior. In goal-directed choice, options can be flexibly evaluated based on the current state of the environment and current goals. That flexibility and generalizability allows agents to make optimal decisions in novel or variable contexts. One specific mechanism, a circuit involving the dorsolateral (dlPFC) and ventromedial prefrontal cortex (vmPFC) has been suggested to provide information about a goal while evaluating choice options and thereby bias choices in favor of self-control.

The current work provides evidence in line with the notion that the dlPFC might introduce or stabilize a bias favoring a current self-control goal. Applying transcranial direct current stimulation (tDCS) showed that impeding the neural processing in dlPFC decreased the effective use of self-control in service of following a health goal. Conversely, facilitating information processing and propagation in the same area interacted with existing strategies to restrain dietary behavior and increased self-control in those individuals that were regularly applying such strategies. Taken together, this suggests that the dlPFC is causally involved in goal-directed self-control decisions.

A second study tested the influence of stress on self-control efficacy. This study showed that the effective decrease in self-control after stress may result from a combination of two processes: increased signaling of immediately accessible reward and a decreased regulatory signaling in favor of the self-control goal by a decrease in coupling between the dlPFC and vmPFC during self-control challenges.

The third study explored possible improvements in predicting an individual's future use of dietary self-control by combining behavioral and physiological measures. Its results suggested that resting heart rate variability may serve as a biomarker for self-control abilities and improve the prediction of self-control levels.

Overall, the findings of these studies may have implications for self-control in other health-related domains. Understanding the changes in neural circuits underlying successful self-control behavior may help to better target and test interventions that help individuals maintain control in challenging environments.

List of manuscripts

The dissertation is based on the following research articles:

Study 1:

Maier SU, Raja Beharelle A, Ruff CC, Hare TA. Changing left dlPFC excitability with tDCS modulates dietary self-control. *In preparation*

Study 2:

Maier SU, Makwana AB, Hare TA (2015). Acute Stress Impairs Self-Control in Goal-Directed Choice by Altering Multiple Functional Connections within the Brain's Decision Circuits. Neuron 87(3): 621-631.

Study 3:

Maier SU, Hare TA. Higher heart rate variability is associated with increased resistance to temptation in the face of dietary self-control challenges. *In preparation*

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"Be moderate in order to taste the joys of life in abundance."
Epicurus (341-270 BC)

1. Introduction

Whether and how humans should regulate their wants and needs is a question that scientific scholars have debated at least since ancient Greece. Yet while lifestyle and consumption decisions could only be made in rather narrow bounds in earlier days, modern life confronts everyone with an increasing number of options of what to consume and in which behaviors to invest time and effort. Thus it becomes increasingly important to choose wisely when selecting which wants and needs to satisfy. Self-control is one of the key cognitive mechanisms that enable humans to control their actions.

While an abundance of resources is welcome in principle, some of the mechanisms that humans have developed to survive in adverse environments might turn into obstacles today. Tendencies to seek novelty and minimize energy expenditure were helpful when resources were scarce and only encountered rather erratically, but they are maladaptive when the modern customer strolls through the aisles of megastores that present ample opportunity to shop energy-dense food that the walk to the car and back home to the sofa will not compensate in terms of burnt calories. Both industrialized and developing countries have faced rising rates of obesity and metabolic syndrome in the past decades (James et al., 2000; Ng et al., 2014), causing immense costs to healthcare systems but also to the quality of life for each individual. Moreover, behaviors such as smoking, excessively using alcohol and lack of exercise lead to a substantial increase in global burden of non-communicable diseases such as cardiovascular disease, diabetes and cancer (Smith et al., 2012). This has stimulated interest in research programs that try to understand what underlies self-control and how it could be promoted. Self-control not only affects dietary choice, although this is one of the self-control decisions that we probably face most often in our daily lives. Numerous other health behaviors require self-control, for example the decisions whether to exercise or not, whether to consume alcohol, tobacco or other drugs or remain abstinent. It may also extend

to financial decisions, such as whether to invest more time in one's education and work or to enjoy leisure, whether to save money for retirement or spend it now, and even to the question whether to follow the rules of society or to commit illegal deeds – all these decisions relate to the capacity to use self-control (e.g. Moffitt et al., 2011).

Parallel research programs in economics (Thaler and Shefrin, 1981; Hoch and Loewenstein, 1991; Laibson et al., 1998; Fudenberg and Levine, 2006; Heckman et al., 2006; Ameriks et al., 2007; Heckman, 2007) and psychology (Mischel et al., 1989; Muraven et al., 1998; Gollwitzer et al., 2004; Ainslie, 2005; Duckworth et al., 2007; Casey, 2015) over the last decades have pointed to important correlates and outcomes of self-control, yet the cognitive mechanisms underlying self-control have so far remained elusive. These parallel efforts have been joined by the discipline of neuroeconomics, which aims at investigating the neural underpinnings of self-control behavior in order to delineate different mechanisms of cognitive processing that may be targeted to improve self-control. Various cognitive processes may play a role in self-control, from directing attention to important aspects and keeping unimportant information out of working memory, over assigning values to decision options, up to inhibiting impulses for inappropriate actions (see Section 1.1). Candidates for neural correlates of these aspects of self-control have been identified in a handful of prefrontal cortex areas (see Section 1.4), but we have only started to understand the role they play in orchestrating behavior, putatively as parts of larger networks that evaluate goals and guide decisions.

Self-control is a very flexible human behavior that can serve many different goals, and part of this flexibility might entail that in some contexts, humans do not or cannot use their capacity for self-control effectively. In this thesis, I investigate external and internal influences on the neural correlates underlying goal-directed self-control decisions. Study 1 tests the causal influence of one prominent candidate for a neural correlate of self-control, namely the dorsolateral prefrontal cortex and its potential modulatory role in value computation. Study 2 investigates the effects of acute stress on neural mechanisms underlying self-control success and failure, and Study 3 explores a

possible biomarker for the capacity to maintain self-control in the face of temptation.

In the introductory chapter, I will briefly review the habitual and goal-directed decision systems and the impact of self-control over the life span, explain how self-control requires goal-directed decisions and which neural mechanisms putatively underlie goal-directed self-control in the brain. The second chapter summarizes the studies on transcranial direct current stimulation on the brain's self-control circuits (Study 1), the effects of stress (Study 2), and heart rate variability (Study 3), before I discuss the results in the third chapter.

1.1 Self-control as a fundamental cognitive skill

Self-control is a key skill in life: It helps individuals channel their efforts towards reaching goals that are important to them and that can only be reached by continued effort or by forgoing currently more tempting options. Scholars in philosophy, psychology, economics, and more recently neuroscientists have therefore taken up the task to characterize what underlies this capacity. Walter Mischel's groundbreaking work on delay of gratification in preschoolers that he probed with the so-called Marshmallow Test (Mischel et al., 1989) has spawned several lines of investigation. The Marshmallow Test assesses whether children are able to wait for an additional reward that is delivered after a period of unknown duration or whether they choose to consume one piece of the same reward right away. This rather simple behavioral readout has an impressive predictive power. Several prospective studies (Casey et al., 2011; Duckworth, 2011; Mischel et al., 2011; Moffitt et al., 2011; Schlam et al., 2013) have tracked Mischel's participants and found that childhood self-control predicts life outcomes in adolescence and adulthood across various domains, such as wealth, health, and criminal behavior. Self-control also predicts academic performance (Mischel et al., 1988; Shoda et al., 1990) and may do so even better than IQ (Duckworth and Seligman, 2005; Duckworth et al., 2010). A parallel research program in economics by Heckman and colleagues similarly suggests that self-control promotes success in school and consequently better employment

chances (Heckman et al., 2006; Heckman, 2007). These findings have inspired several research programs that try to pinpoint what underlies the human capacity to postpone gratification in service of an ultimately more worthwhile goal.

Most likely, it is not one particular ability, but rather a number of factors that contribute to successful self-control, both for single decisions and over a lifetime. The most obvious ability needed to execute self-control decisions is *restricting a pre-potent impulse to perform an action* in case it is not appropriate, as for example a laboratory Go/NoGo or Stop-Signal task would measure it. Although the inhibition of behavior comes to mind first, physical impulse control is necessary, but not sufficient for exerting self-control. In many cases, before an impulse to act in a certain way is generated, a more basic process is required. In order to take the best action in novel or variable contexts, an agent needs to *calculate values* for the actions that are feasible so that she can determine which action yields the best outcome. In the service of self-control, determining the best outcome requires *factoring in long-term goals* that are only realized in the future.

This raises the question of what could bias an agent's ability to factor in her long-term goals. Factors such as *directing attention* (and/or *altering the cognitive representation* of a tempting object (Rodriguez et al., 1989; Sethi et al., 2000; Kaplan and Berman, 2010)) have early been identified as important aspects that may shape processing of self-control problems. One characteristic of cognitive control processes (Cohen et al., 1992; Desimone and Duncan, 1995; Casey et al., 2000; Miller and Cohen, 2001) is the ability to suppress attention to or override irrelevant information and behavioral responses that do not serve the current task optimally. Thus, self-control may be easier to use for those individuals who are able to keep unwanted information out of their working memory (Berman et al., 2013), as irrelevant information might otherwise interfere with determining and executing the best action. Another basic requirement is to overcome or alter one's own *expectation* that the desired outcome would be too effortful or unlikely to achieve and thus not worth the effort (Shenhav et al., 2013). Yet forming this expectation requires again comparing costs and benefits of certain action plans and thus relies on the basic

process of *assigning values to the decision options*. Evaluating the available options for consumption or other actions is therefore at the heart of single self-control decisions. In this thesis, I investigate how the brain constructs value-based decisions in a way that supports self-control.

1.2 Habitual and goal-directed decisions

The study of decision-making poses a conundrum: While humans intend to follow a certain goal and verbally report attempting to do so, their behavior often mirrors the opposite of their intentions. Despite our best intentions, what we consider being the best course of action is not always what we end up doing, and some behaviors even drive us farther away from the goals that we set for ourselves. Almost everyone has experienced such opposing forces when trying to make a deliberate decision, and this makes theories that propose separate systems for deliberate and automatic choices intuitively appealing. It is not surprising that many authors in the psychology and economics literature assume a divide between fast, automatic, and slow, deliberative processing systems in human decision-making (Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977; Sloman, 1996; Kahneman and Frederick, 2002; Gollwitzer et al., 2004; Kahneman, 2011). The terminology may differ slightly, but essentially the deliberative processing is associated with control, assumed to operate only after being recruited by reflective thought, and considered to be modifiable by conscious thought. On a parallel route, automatic processing is assumed to operate continuously, reacting to changes in the environment similar to a reflex, often with little conscious control.

Camerer, Loewenstein and Prelec (2005) introduce this approach in the neuroeconomics literature. They argued that in order to model decision-making, theories have to not only consider what consciously registers as the costs and benefits of decision options, but also have to account for automatic processing that may contribute to the outcome of decisions. Their framework points out that automatic processes in the brain may exist because they "solve problems of evolutionary importance" (Camerer et al. (2005), p. 11), and this may result in actions being initiated before conscious deliberation and volitional control could take place at all. Underlying their argument is the idea that certain mechanisms

might have evolved to support typically successful behaviors, for example a tendency to register novel stimuli as rewarding and seek out novel experiences for information gain. To complicate matters, the machinery that runs these calculations is costly to operate in terms of energy consumption, and several authors have pointed out more recently that one of the governing principles of how the brain organizes its decision-making might be to minimize energy expenditure or effort (Botvinick and Rosen, 2009; Kool et al., 2010; McGuire and Botvinick, 2010; Kool et al., 2013) or even drive behavior towards securing more energy resources, as Peters (Peters et al., 2004; Fehm et al., 2006; Peters, 2011) proposed in his "selfish brain" hypothesis. Both might shape the functioning of automatic processes that might be geared towards securing physical needs. In addition, Camerer et al. (2005) point out that another important modulator of decision-making might be emotional processing. Affective systems (LeDoux, 2012) may interact with volitional, reflective processing on a neural level (Schwarz, 2011).

As Camerer and colleagues emphasize, accounting for these interactions between "automatic" and "controlled" systems (Schneider and Shiffrin, 1977; Camerer et al., 2005) should increase the predictive power of decision-making models. The neuroeconomics literature reflects this consideration in its concepts of habitual and goal-directed control systems (Dolan and Dayan, 2013). Differences between these systems partially depend on how these systems learn the values of rewards, but extend beyond learning to the question of how they construct decision options, using either a retrospective (habitual) or prospective (goal-directed) mechanism. Usually the systems are discussed in close connection to each other; whether their outputs are competing or whether each system is deployed as needed by a "meta-controller" is an unresolved question. What sets them apart is the type of information they can process.

Rangel, Camerer and Montague (2008) propose that three separate valuation systems co-exist: *Pavlovian* systems cover a limited scope of behaviors, in which particular stimuli in the environment evoke prepared (either innate or overtrained) behavioral programs. *Habitual* systems can be formed for a wider range of behaviors, for which courses of action are learned through repeated trial-and-error and are associated with a relatively stable value that corresponds

to the reward for performing this action in the past. Habitual systems learn by forming associations between obtained rewards and actions performed to get these rewards given a certain state of the world, but this implies that the habit system cannot consider consequences of actions that have not been experienced yet. *Goal-directed* systems eventually allow the brain to flexibly assign values by computing associations between actions and expected outcomes and evaluating the rewards that are associated with different outcomes.

Given the plurality of possible control systems, the brain needs to arbitrate between their outputs if their proposed action plans disagree. Daw et al. (2005) have shown that this arbitration might be solved by relying on the system that has the most accurate (i.e. least uncertain) estimate at any given time, which should favor the habitual system when there has been sufficient experience with a decision problem, and the goal-directed system in novel situations or under rapidly changing environmental conditions.

For the goal-directed control system, Rangel and colleagues (2008) have suggested a framework for investigating the neurobiology of decision-making that characterizes basic computational steps for choosing between options based on their value: The agent needs to represent a set of feasible actions and her current internal and external state. She then can calculate a value for each action, given the internal and external states, and in a next (or concurrent) step select the action with the highest overall value. After carrying out the action, she can evaluate the outcome and categorize how desirable the outcomes and states were that followed the action. This information feeds back into a learning loop that updates the representation, valuation and action-selection processes.

Notably, the type of cognitive architecture that Rangel and colleagues propose allows for a rather sophisticated optimization of behavior. It is an important theoretical feature that the agent can represent and calculate the value of decision options based on their utility. Being able to assign utility is crucial, as different actions may lead to the same primary goal-state (for example, when hungry, one could eat an apple or a chocolate bar and achieve the goal state of being satiated). If the agent was constrained to evaluating only the binary outcome of whether the primary goal (satiation) was achieved or not and could not make more fine-grained distinctions about the utility levels for each

outcome, she could not make a precise cost-benefit analysis between outcomes and refine her actions to achieve the desired outcome in an optimal manner. Examples of optimal actions are those made with less effort, more quickly, or more reliably (Russell and Norvig, 2003). In the specific case of food consumption decisions, an optimal choice may be choosing the option that conveys a higher benefit in terms of health, versus choosing a higher hedonic benefit in terms of taste.

Consequently, in order to understand decision-making in humans, we need to understand better how individuals construct the utility (or, in neuroeconomics, the *subjective value*) they assign to different decision options. Several aspects may modulate the construction of a subjective value for each option. Rangel and colleagues (2008) point out examples of modulators, such as risk (when the outcome can only be obtained with a known probability), uncertainty (when the probability of outcome delivery is unknown) and time discounting (which decreases the attractiveness of an outcome based on how far in the future it will be obtained). What governs how strongly these modulators are operating is still unknown, but possible candidates, for example in time discounting, are external situational factors such as stress (Fields et al., 2014; Hollon et al., 2015), or internal states, such as emotional (Wilson and Daly, 2004; Lerner et al., 2013; Phelps et al., 2014; Lempert and Phelps, 2015) or metabolic state (Tobin and Logue, 1994). Considering far-reaching consequences of actions might be harder in some situations than others. To understand how individuals master self-control challenges, a better understanding of person-situation interactions (Shoda et al., 2007) is needed. The impact of situational modulators of self-control such as emotions or stress has been recognized and investigated in behavioral studies during the past decades, but for a more complete understanding of inter-individual differences in reactions to these modulators, we might need to turn to the neural level in order to detect changes in the cognitive mechanisms that explain when and why some individuals begin to fail in using self-control when experiencing these states.

1.3 Self-control in goal-directed decisions

During the calculation of values for choice outcomes, self-control goals can be explicitly factored in (or ignored), as goal-directed and habitual systems use different types of information: While habitual systems per definition cannot consider state-dependent future consequences of actions, goal-directed systems can factor in such considerations. This ability to prospectively construct values with bearing future consequences in mind is an important prerequisite for flexibly deploying self-control across a wide range of situations. Although predictable self-control challenges could be addressed by improving habitual control (and certainly most people can identify challenges they often face and come up with strategies to circumvent them), many self-control challenges require calculating the values of choice outcomes on the fly.

In order to use self-control in these novel situations, stimulus values need to be adjusted for long-term goals: Before an individual can act, she needs to determine the best course of action given her self-control goal, and this requires her to appropriately weight attributes of the choice options. For example, in food choice, the agent might have to choose a healthier food despite its potentially less pleasant taste in order to obtain the ultimately more beneficial outcome of maintaining health that can only reached by giving up currently tempting, but overall less rewarding options. Solving the choice problem requires integrating aspects such as cost and benefit of each available action depending on the current situation, and ranking the options along their reward value in order to pick the outcome with the highest value.

For the sake of simplification, this work follows the approach of Rangel and coworkers (Rangel, 2013; Rangel and Clithero, 2014) in considering the calculation of stimulus (i.e. outcome) values, action costs, and action values (i.e. the net value of stimulus value – action cost) as at least partially separable neural processes. Rangel and Clithero (2014) summarize in their model for simple choice (e.g. the choice between two food options) that the brain encodes *stimulus values* of potential outcomes weighted according to the probability with which the outcomes are obtained and temporally discounted in case reward delivery is delayed. *Action costs* are encoded separately and scale with the subjective value

of taking the action to obtain the outcome. *Action value* signals putatively integrate action costs and stimulus values (Rangel and Hare, 2010).

In this thesis, only the calculation of stimulus values will be investigated as this lays at the heart of evaluating decision options, without considering the calculation of action costs. In order to accurately determine stimulus values with regard to a self-control goal, agents need to factor in how well their options correspond to this goal. I use versions of a dietary self-control paradigm (Plassmann et al., 2007; Hare et al., 2009) to assess this capacity. The paradigm makes the basic assumption that taste and health aspects are representing short-term and long-term rewards. This good-based choice paradigm has advantages over monetary inter-temporal choice tasks because its measurement of self-control is not confounded by aspects specific to a monetary outcome, such as risk perception (Andreoni and Sprenger, 2012; Epper and Fehr-Duda, 2015) that could change the choice function regardless of self-control if the agent is not entirely sure that the money will be delivered in the future, and is also immune to current financial budget constraints of the agent (who might plan on the money earned in the study for paying expenses in the near future). Both risk preferences and budget constraints might prevent choosing the delayed outcome, but have nothing to do with the agent's ability to use self-control in principle. Thus, the dietary choice paradigm provides a cleaner measure of self-control in these regards.

Moreover, dietary choice is comparable to other health behaviors that involve consumption decisions about a tempting stimulus substance, such as nicotine, alcohol or drugs of addiction. The major advantage of food, however, is that the circuits underlying deliberate self-control decisions can be probed with actual consumption decisions that are ethically unproblematic and can therefore regularly be administered in laboratory settings.

The paradigm is incentive-compatible, i.e. it is in the participants' best interest to answer honestly. To make the choices relevant, one of the trials is randomly chosen to be realized in the end and participants know that they will have to eat the food item they chose on the selected trial. This prevents over-reporting of the intention to use self-control that is possible with other measures such as questionnaires, when answers are given for example due to social

desirability, but do not bear consequences (Logan et al., 2008). Under-reporting (i.e. adopting a strategy of not choosing any foods) can be prevented by adding as a rule that in case participants fail to choose within the allocated choice period and this trial is selected for realization, a random draw between the alternatives on this trial determines what the participant gets to eat in the end, so it is again in the participant's best interest to express her preference honestly. Moreover, a waiting period of 30 minutes is added at the end of each experiment, during which the participants may only consume the food they chose during the study, which makes the choices more meaningful because participants cannot immediately buy other food.

The working definition of self-control I use here, based on this paradigm, is the one of Hare et al. (2009): In order to succeed in self-control, participants have to forgo the immediate gratification of eating a tasty, yet less healthy food item, in order to receive an ultimately superior outcome (health) when they achieve their long-term goal of maintaining a healthy diet.

In order to explain how self-control is harmed or promoted by situational modulators, we need to understand what changes the subjective valuation of choice options, i.e. what makes the taste and health aspects more or less salient when an agent considers her options. In sum, modulations could change self-control via three channels: first, by increasing (or decreasing) the influence of rewards that correspond to short-term goals; second, by decreasing (or increasing) the influence of regulatory mechanisms that factor in long-term goals; third, by doing both simultaneously. A fourth way in which self-control might be hurt is that the mechanism integrating short- and long-term aspects of decisions itself might be broken, but this seems unlikely in a healthy population. As I tested only healthy participants in my studies, I will focus on discussing the first three questions and their potential neural mechanisms.

1.4 Neural mechanisms underlying goal-directed self-control

Goal-directed self-control requires neural processes to identify goals, calculate stimulus and action values, detect the need for regulation, and orchestrate the execution of regulatory processes. The implementation of self-control goals thus

builds on the functions of *working memory* (Arnsten and Jin, 2014; Brunoni and Vanderhasselt, 2014; Wesley and Bickel, 2014), *attention* (Arnsten and Rubia, 2012; Squire et al., 2013; Solbakk and Lovstad, 2014; D'Esposito and Postle, 2015; Spencer et al., 2015), *planning* (Barbey et al., 2009; Mushiake et al., 2009; Fuster and Bressler, 2015; Spiers and Gilbert, 2015), *shifting* between task sets (Robbins, 2007; Rossi et al., 2009; Kehagia et al., 2010), and *response inhibition* (Aron et al., 2003; Aron et al., 2004, 2014). All of these functions have been associated with the prefrontal cortex (PFC).

The anatomical structure of the PFC is a relatively recent development in evolutionary history. It is most refined in primates, or even unique in case of the granular dlPFC (Preuss, 1995; Wise, 2008), and human brains show a more dense packing and connectivity of cells in the frontal pole that is lacking in other primates (Semendeferi et al., 2011). This allows solving more complex problems. Koechlin (2014) suggests three layers of inference: The basic function is to reactively infer changes in the environment after experiencing outcomes. Additionally, the evolutionary refinement of lateral prefrontal cortex in primates allows them to make proactive inferences by recognizing contextual similarities in their environment and thus switching behavioral strategies before an outcome occurred, which may help to prevent experiencing negative outcomes. A third layer of inference, unique to humans and putatively drawing on the frontopolar cortex, is counterfactual reasoning that helps inferring when to switch a behavioral strategy. The neural circuitry in the PFC allows adapting behavior flexibly to changes in the internal state of the individual and its external environment. During the maturation of the individual organism, PFC function develops late, and within the human PFC, the dlPFC is the last structure to mature at the end of adolescence (Gogtay et al., 2004).

The PFC connects to sensory systems, motor systems and subcortical structures, and with its anatomical and functional connections it is „well positioned to coordinate a wide range of neural processes“ (Miller and Cohen (2001), p. 168). Ample correlative evidence suggests that the lateral PFC is involved in self-control, both in monetary inter-temporal choice (McClure et al., 2004a; Fudenberg and Levine, 2006; Berns et al., 2007; Brass and Haggard, 2007; Knoch and Fehr, 2007; McClure et al., 2007; Ballard and Knutson, 2009;

Bickel et al., 2009; Luo et al., 2009; Xu et al., 2009; Mitchell et al., 2011) and dietary choice tasks (Hare et al., 2009; Hare et al., 2011a; Hare et al., 2014; Foerde et al., 2015).

Many authors take the representation of goals and actions how to reach these goals as the core of this cognitive control function (Cohen and Servan-Schreiber, 1992; Passingham, 1993; Grafman, 1994; Wise et al., 1996; Miller, 1999; Braver and Cohen, 2000; Frank et al., 2001). The PFC is thought to produce "bias signals" (Miller and Cohen (2001), p. 171) that guide the execution of responses, but also memory retrieval and for example the perception of emotions in case perceptions are ambiguous or when several responses are competing and the stronger response tendency would be inappropriate and needs to be inhibited.

For goal-directed self-control choices, three regions in the prefrontal cortex could be considered integral in generating, routing, and processing signals (also see Shenhav et al. (2013) and Kelley et al. (2015)). One is the *vmPFC*, which has been hypothesized to calculate fine-grained stimulus values in order to determine the optimal outcome of a choice (Kable and Glimcher, 2007; Rangel, 2013; Grueschow et al., 2015), second, the *dlPFC,* for which a number of roles have been proposed: retrieving the context of a choice and storing current goals in working memory, implementing control by biasing attention, and modulating the calculation of stimulus values, the choice, and the execution of appropriate actions (MacDonald et al., 2000; Koechlin et al., 2003), and third, the *ACC* (particular its dorsal part that comprises the cytoarchitectonic areas 24 and the dorsal part of area 32) that has been hypothesized to detect and define the need for regulation based on vmPFC value processing and relaying this need for control to the structures helping to implement it, for example the dlPFC (Shenhav et al., 2013).

In the following, I will focus on the question of how a goal could factor into a decision, and thus examine one candidate region, the dlPFC, and its connectivity with the vmPFC at the time of choice in order to assess its potential for modulating choices in favor of self-control goals. I will review evidence for the vmPFC and dlPFC being involved in self-control decisions per se, and

describe what is known about a possible modulatory connection between these two regions.

vmPFC. Converging evidence in humans, monkeys and rodents has associated the vmPFC (and the overlapping areas of the medial OFC) with the representation and calculation of stimulus values. The value representation in vmPFC distinguishes potential outcomes according to their attractiveness, which is an important feature if an agent wants to find the optimal choice. BOLD activity in the medial OFC during the receipt of a reward has been shown to scale with the pleasantness of enjoying the reward (Blood and Zatorre, 2001; Anderson et al., 2003; de Araujo et al., 2003a; de Araujo et al., 2003b; Kringelbach et al., 2003; Small et al., 2003; McClure et al., 2004b; de Araujo et al., 2005). This has not only been observed for primary rewards, such as food, but also secondary rewards such as money (Breiter et al., 2001; Knutson et al., 2001; Zink et al., 2004), social outcomes (Izuma et al., 2008; Hare et al., 2010; Lin et al., 2012), art (Abitbol et al., 2015), attractive faces (O'Doherty et al., 2003), and even imagining hypothetical outcomes (Bray et al., 2010).

In theory it might be possible that stimulus values are learned through repeated experience and then just retrieved from storage at the moment of choice. However, humans routinely construct prospective stimulus values, and can even integrate features that are usually not encountered together in order to determine whether they might like to choose an object with these properties. Barron, Dolan and Behrens (2013) nicely demonstrated this with the example of items such as “tea-jelly” that has the taste of tea, but the texture of jelly. The attribute integration model of stimulus value computation presented in Rangel (2013) and Rangel and Clithero (2014) assumes that stimuli are complex bundles of basic attributes and animals evaluate any stimulus, known or novel, by learning the value of basic features and then integrated these attribute values into an overall stimulus value when they need to choose. The current working assumption is that this integration happens in the vmPFC. A stimulus value in this model is a linear weighted sum of all attributes that were considered (Rangel and Clithero, 2014). Consequently, a critical question is what determines the weighting of stimulus attributes. Assuming that the vmPFC receives inputs via several channels about the basic features of a food stimulus, the question

arises with regard to our food choice example what could bias the decision process in favor of health aspects that promote our self-control goal of eating healthy: Is it the amount of signal that the vmPFC receives on taste and health aspects of the options, its clarity, or both? Can the signal be changed in favor of one aspect, for example by deliberately attending to it? Considering the example of food choice, this might be particularly important if one stimulus tastes a lot better than the other, but is less healthy. How could a neural decision mechanism then tip off the balance still in favor of health?

One suggested mechanism to achieve biasing the decision process in favor of a goal is a modulatory connection between the dlPFC and vmPFC. Plenty of studies have found the dlPFC and vmPFC involved in value-based decisions (for an overview of the literature, see Rangel and Clithero (2014)). Among the modulatory connections that influence value computation during choice, the dlPFC with its roles in attention and working-memory seems the best candidate node for biasing value-calculation towards current goals.

dlPFC. Causal evidence for a dlPFC involvement in control has been provided in lesion mapping studies: a recent meta-analysis by Gläscher et al. (2012) revealed a functional network including dlPFC and ACC in cognitive control. However, the results from lesion mapping remain mixed, as damage to the dlPFC does not necessarily compromise choosing delayed rewards in inter-temporal choice (Fellows and Farah, 2005). Temporary inhibition or improvement of neural signaling in the dlPFC with the help of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) provided corroborating evidence for an involvement of the dlPFC in the regulation of craving and the choice of delayed outcomes (for a review of the literature see Study 1 in the Appendix), however. Anatomical differences may also play a role: decreased gray matter volume in lateral PFC has been associated with greater impatience in inter-temporal choice (Bjork et al., 2009). While these findings together strongly suggest that dlPFC plays some role in self-control and is potentially causally involved, its exact function(s) remains elusive. Caution is warranted in interpreting results that employ different paradigms for measuring self-control. As successful cognitive control may rely on a number of supporting functions (such as attention, working memory etc.), these functions might be

involved to a different degree in various tasks used to measure self-control, which may yield inconclusive evidence (Duckworth and Kern, 2011).

Moreover, the dlPFC is a rather large area and different roles have been postulated for its anterior and posterior regions: Koechlin et al. (2003) suggested a gradient in cognitive control in the lateral prefrontal cortex (lPFC), in which the rostral lPFC would subserve episodic control and deal with past events, the caudal lPFC would produce contextual signals, caring about stimuli and their context, and the premotor cortex would care more about the stimulus and adequate motor responses. A study by Cieslik et al. (2013) using meta-analytic connectivity modeling suggested that the anterior dlPFC has a role in attention and action inhibition, while the posterior part has a role in working memory and action execution.

Earlier studies with the dietary self-control paradigm used in this work have identified dlPFC and vmPFC functioning as critical for self-control. It has been assumed that in dietary choices that require self-control, i.e. overcoming one's own taste preferences in order to choose a food that supports an overall better health outcome, the decision network needs to integrate the health and taste value of each food option in order to determine which one has the highest overall value. Hare et al. (2009) found that dieters who preferred less healthy, tastier foods represented only taste value in the vmPFC, whereas dieters who chose more of the healthier, less tasty foods represented both health and taste value. Hare and colleagues identified a functional connection between the left dlPFC and the vmPFC as a potential pathway to strengthen the representation of the health information in the vmPFC during choice. In a subsequent study, Hare et al. (2011a) showed that a reminder to focus on the health aspects of choice options increased the number of healthier food choices and this increase correlated with the strength of the connectivity between dlPFC and vmPFC at the time of choice.

Before describing the evidence for a modulatory dlPFC-vmPFC mechanism in more detail, alternative theoretical accounts that suggest other roles for the dlPFC will be briefly revisited. In the search for neural correlates of goal-directed self-control, the dlPFC features a prominent role. Currently, five major accounts involve dlPFC as a substrate of self-control: Fehr and colleagues

(Knoch and Fehr, 2007; Figner et al., 2010) hypothesized a role in inhibition that has been strongly challenged by Aron and coworkers (2014), whereas the other four accounts assign a preparatory role, but not the final execution of the control to the dlPFC. Most of these other accounts in the neuroeconomics literature assume a role of the dlPFC in value computation. The account hypothesizing patient versus impatient systems (McClure et al., 2004a; Berns et al., 2007; McClure et al., 2007) is set apart by its prediction that the dlPFC might calculate a separate value for the patient outcome, while the accounts on the expected value of control (Shenhav et al., 2013) and the modulation of value computation (Rangel, 2013) are both assuming that the dlPFC biases regulation by creating a goal-context that the options under consideration need to match. Similarly, although tested on more abstract task sets, the adaptive versus stable control systems account by Dosenbach and colleagues (Dosenbach et al., 2006; Dosenbach et al., 2007) sees the dlPFC as a part of a larger fronto-parietal network serving the adaptation of control (for example in a goal context), whereas the stabilization of control is hypothesized to involve a cingulo-opercular network.

dlPFC-vmPFC modulation. For my current purpose to better understand whether the dlPFC may exert a modulatory influence on the vmPFC during value computation in order to promote choices based on self-control goals, the approach of Rangel and colleagues presents the most parsimonious mechanism. Initial evidence speaks in favor of their model. Causal evidence for a modulatory connection between the vmPFC and the dlPFC in normative decisions was found by Baumgartner, Knoch, Hotz, Eisenegger and Fehr (2011): they showed that lesioning the right dlPFC temporarily by transcranial magnetic stimulation (TMS) decreases activation in dlPFC and vmPFC as well as their functional connectivity. Further evidence for a functional connection of both areas comes from a positron emission tomography (PET) study by Cho and Strafella (2009) that found higher dopamine D2 receptor binding in the ipsilateral mOFC, subgenual ACC and pregenual ACC after facilitating left dlPFC activity with high-frequency rTMS, but did not observe an analogous effect after stimulating the right dlPFC.

Importantly, both dlPFC and vmPFC most likely are part of larger networks, as for example Dosenbach and colleagues suggested in their account on cognitive control. Synchrony of activation may play a role in successfully using self-control networks. A follow-up fMRI study on the participants of Mischel's original delay of gratification studies by Berman et al. (2013) suggests that individuals who show high self-control abilities in their daily lives express stronger connectivity between brain regions and more focused BOLD activation than individuals with low self-control levels. Investigating measures of functional connectivity thus provides vital insights how and why the effective use of self-control might differ across situations.

2. Summary of the experimental strategy

Self-control choices may depend on context factors, both internal and external (Heatherton and Wagner, 2011; Lempert and Phelps, 2015). In order to understand in which circumstances individuals consider long-term goals that promote self-control and when they do not, I experimentally introduce potential modulators and focus on their impact on subjective value computation in the computational framework of Rangel and colleagues presented in the previous chapter. To examine how the internal state of the agent or reactions to the external situation may change her capacity to evaluate decision options, both correlative and causal methods will be used. The studies presented in this work serve two goals: First, to test whether goal-directed self-control in the dietary choice paradigm causally requires the dorsolateral prefrontal cortex (dlPFC) and second, how the dlPFC's contribution to value-computations underlying self-control decisions is enhanced or diminished. First, I apply a causal intervention, transcranial direct current stimulation, to the dlPFC in order to probe whether it indeed biases decisions in favor of self-control. Then I selectively challenge the proposed modulatory brain circuit between dlPFC and vmPFC with one specific external modulator, stress. Lastly, I investigate a physiological systems level biomarker, heart rate variability, in order to test its potential to predict inter-individual differences in self-control.

Previous fMRI work has provided correlative evidence for an involvement of the dlPFC in self-control. Here, I causally probe the contribution of the left dlPFC to value computation when choices need to match self-control goals. In Study 1, anodal, cathodal, and sham transcranial direct current stimulation (tCDS) is applied over the left dlPFC. This allows me to test the causal involvement of the dlPFC in the value computation process and potential ways to augment or diminish dlPFC contributions that increase or decrease self-control.

Study 2 tests the influence of an important external modulator of self-control present in everyday life: In a randomized between-subjects design, participants have to make self-control choices after they have experienced a moderately stressful situation or a control condition. By collecting blood oxygen level dependent (BOLD) functional magnetic resonance images (fMRI), I can relate the impact of both emotional and hormonal aspects of the stress reaction to changes in brain metabolism to map where and when neural activity in the stressed participants deviates from unstressed controls when they try to use self-control in order to follow a health goal.

In Study 3, I investigate a physiological factor that may potentially serve as a marker of differences in the individual capacity to react to self-control challenges: Heart rate variability (HRV) at rest, collected before the participants underwent the stress treatment of Study 2, predicts their later performance in the self-control paradigm. HRV also relates to differential BOLD activity in the vmPFC during self-control choices.

2.1 Study 1: A causal probe of left dlPFC modulation of self-control

Background

The left dlPFC has consistently been related to subserving goal-directed decisions (Hare et al., 2009; Hare et al., 2011a; Hare et al., 2011b; Harris et al., 2013; Hare et al., 2014; Rudorf and Hare, 2014; Foerde et al., 2015). Hare and colleagues have suggested that in the dietary choice paradigm, the left dlPFC might support self-control by biasing the calculation of integrated stimulus values towards a health context (Hare et al., 2009; Hare et al., 2011a). Yet it

remains unclear whether the dlPFC is causally involved in a neural network underlying goal-directed self-control when these integrated stimulus values are calculated in order to make decisions. In order to test whether facilitating and impeding neural activity in the left dlPFC increases and decreases the frequency of self-control choices respectively, anodal or cathodal transcranial direct current stimulation (tDCS) was applied while participants made dietary self-control choices that pitted immediate taste rewards against long-term health goals.

Methods

90 participants were included in the study (stimulation groups: Anodal (30 participants, 15 women), Cathodal (29 participants, 16 women), and Sham (31 participants, 14 women)). All participants liked and regularly consumed snack food, making it likely that they could be tempted by the presented snack foods. Upon arrival, participants rated 180 foods for taste and health and completed a battery of control tasks that addressed potential changes in working memory (digit span task), impulse control (stop signal reaction time task), delay discounting (inter-temporal choice task), and hunger levels (indicated on a visual analog scale) that might account for changes in self-control (see Methods in Appendix A). After these tasks, all participants signed a health goal statement (see the Methods / Procedure in Appendix A) indicating whether they would try to choose the healthier food option on each trial in the upcoming food choice task. In the analyses, only participants who consented to following the health goal were included.

In order to address within-participant changes, participants were asked to make 60 food choices before the stimulation started. The choice paradigm in this study was tailored to the individual taste and health ratings such that all of the choices contained self-control challenges, i.e. the healthier item was not the tastier one, but we varied the degree of taste temptation that participants experienced based on their taste ratings. Before each block of 10 trials started, a food item was presented for 3 seconds that served as alternative for this block, should the participant not wish to choose the item presented on the screen within the block. In type A choice blocks, the alternative was strictly healthier

and less tasty than the items presented in the block, so participants had to say "no" to the items within the block in order to comply with their health goal. In type B choice blocks, the alternative was strictly tastier and less healthy than the items presented in the block, so participants had to say "yes" to the items presented during the block in order to choose healthier. Both block types were presented in a pseudorandom order, counterbalanced between stimulation groups. During stimulation, participants made another 120 choices. Participants had 3 seconds to make their decision. From all choices made during the study, one was randomly chosen to be realized and participants knew that they would be asked to eat what they chose on this trial. In order to further incentivize choice, one of the two alternatives was selected randomly if a trial was drawn for realization on which the participant had failed to answer within 3 seconds. Following the choices, participants repeated the control tasks. Lastly they filled in a battery of psychometric questionnaires (Three Factor Eating Questionnaire (TFEQ), Cognitive Reflection Test (CRT), "Big Five" personality traits (NEO-FFI), and questions addressing socio-economic status) while waiting for their food payoff.

A mixed-effects binomial regression model was used in order to assess influences on self-control failure (i.e. choosing the tastier, less healthy item). The model estimated potential interactions between trial-level (absolute taste and health differences between the alternative and the item on the screen, and a dummy regressor for stimulation that coded stimulation trials as ones and baseline trials as zeros) and participant-level variables (stimulation condition, restrained eating score) while controlling for body mass index. In order to capture the individual increase in self-control failure rates within participants, the model included random intercepts and slopes for the participant-level effects and the effect of taste and health differences (see Figure 4 in Annex A).

Results and conclusions

At baseline, none of the stimulation groups differed significantly from the sham group in their performance. Stimulation influenced self-control behavior differentially as a function of polarity. Self-control decreased under cathodal compared to sham stimulation. For anodal stimulation, the model revealed no

main effect, but an interaction with the restrained eating score. High-restrained eaters in the anodal group showed a greater improvement in self-control under stimulation relative to the cathodal group.

The effect that cathodal tDCS over the left dlPFC impaired self-control was in line with the hypothesized role that the dlPFC facilitates self-control in goal-directed choice. Participants in the cathodal group performed worse under stimulation compared to their baseline. Therefore the information conveyed by dlPFC neurons appears to help improve self-control, and impeding the propagation of this information effectively reduces the use of self-control.

In line with previous findings, the effect of the anodal stimulation depended on the individual expression of a restrained eating trait as identified by the restrained eating scale of the Three-Factor Eating Questionnaire. State-dependency has been described earlier for anodal stimulation (Silvanto et al., 2008; Silvanto and Muggleton, 2008; Silvanto and Pascual-Leone, 2008; Weigand et al., 2013). It suggests that the effect of stimulation may differ depending on which cognitive functions are currently executed. In the case of restrained eating, this may entail that the stimulation may have enabled restrained eaters to better use their existing neural pathways or food choice strategies.

No effects of tDCS stimulation on any of the control tasks were observed. Stimulation also did not induce shifts in taste or health ratings. Taken together, this suggests that the changes were not due to altering a more basic cognitive function that supports self-control, but were specific to executing self-control. In sum, the results suggest that the left dlPFC is causally involved in a neural circuit that supports self-control.

2.2 Study 2: The impact of acute stress on self-control

Background

Stress has widely been reported to affect motivated behavior (Hollon et al., 2015), and recent studies have suggested that under acute stress, goal-directed control is abandoned in favor of habitual control (Schwabe and Wolf, 2009; Schwabe et al., 2010b, a; Schwabe and Wolf, 2010; ter Horst et al., 2012). Yet the mechanism that underlies these behavioral changes is still unclear. During acute

stress, noradrenaline secretion is increased via activation of the sympathetic-adrenal medullary (SAM) stress axis that reacts fast, while cortisol secretion is effected via the hypothalamic–pituitary–adrenal (HPA) axis that responds more slowly to stressors. The HPA axis has been suggested to particularly respond to characteristics such as ambiguity regarding potential outcomes, novelty, unpredictability, and uncontrollability of a situation, as well as personal factors such as anticipation of negative consequences for one's social image (Mason, 1971; Dickerson and Kemeny, 2004). Schwabe et al. (2012) demonstrated in a pharmacological study that the neuromodulator cortisol and the neurotransmitter noradrenaline have to be administered in combination in order to impair goal-directed learning and behavior, whereas administering either one alone did not effect this change. Using the same pharmacological manipulation as Schwabe and colleagues together with a cognitive reflection test, Margittai et al. (2016) observed that exogenous cortisol administration caused a shift from deliberate cognition towards automatic and intuitive but incorrect answer patterns.

The question thus arises whether stress also compromises the ability follow self-control goals, and via which channels self-control might be impaired. In the dietary self-control paradigm that was introduced in Section 1.3, self-control might be compromised by 1) emphasizing taste more, 2) emphasizing health less, or 3) both happening at the same time when making a choice. Regarding stress and dietary choice, evidence has been reported in favor of point 1) in regard to an increased taste representation after stress (for a review see Adam and Epel (2007)), but no conclusive evidence exists on point 2), how stress interferes with the brain's capacity to maintain regulatory self-control signals that could counterbalance increased taste signaling. Particularly it is unclear whether stress affects a modulatory connection between the dlPFC and the vmPFC at the time of choice.

To address the question of how stress affects neural mechanisms of self-control in the face of temptation, I developed a version of the dietary self-control paradigm that confronts participants with various degrees of taste temptation when they choose between two food items while trying to follow a health goal. The task controls for the capacity to identify recommendations that violate the

goal of eating healthy, which allows controlling for the possibility that stress might have compromised a capacity to use rule-based cognitive control in general. Extending the model of Adam and Epel (2007), I hypothesized that an increased number of self-control failures under stress could be due to increased reward signaling for the taste of the foods, or due to decreased regulatory signaling for choosing the healthier food, or both.

Methods

I investigated the effects of acute stress on self-control in a between-subjects fMRI study, in which participants were randomly allotted to a stress treatment (n = 29) with the Socially Evaluated Cold Pressor Task (Schwabe et al., 2008) or a control treatment (n = 22) that took place right before the fMRI scans. All participants had been selected because they maintained a health-oriented lifestyle, but also liked and regularly consumed snack food, and thus would likely experience self-control challenges during the choice task. The self-control paradigm asked participants to select one of two items on the screen for eating at the end of the study. Participants were reminded of their goal of choosing the healthier item by a small health icon depicted during the inter-trial interval. Based on previously collected health and taste ratings, I identified trials in which participants successfully mastered self-control challenges and chose the healthier, but less tasty food, and trials in which they failed and chose the tastier, but less healthy food item. Additionally, the task contained recommendations about which item was healthier. A recommendation was depicted as a white frame around the item. This element of the task showed whether the participants were able to identify and overcome misleading information. Most of these recommendations (120) correctly identified the healthier food, but 60 pointed out the less healthy food, and 30 trials without a recommendation served as a baseline for comparison. Participants were told up front that the recommendations could sometimes be wrong and that they should try to maintain their health goals in the face of incorrect recommendations.

Preprocessing and first level-analysis for the fMRI data were carried out using the statistical parametric mapping software suite (SPM8). The raw fMRI data were realigned and unwarped, segmented according to the participant's T1

structural scan, spatially normalized and smoothed. I used a generalized linear model (GLM) approach to analyze the participant-level data and compared between-group differences and correlations with individual stress responses (perceived stress level and cortisol levels) on the group-level using non-parametric permutation tests from the FMRIB software library (FSL, version 5).

Results and conclusions

Behaviorally, stressed participants failed to use self-control more often than the control group. This was particularly pronounced for choices that required the highest level of self-control because they presented the greatest taste temptation. Both stress and control groups, however, tried to follow the health goal and were generally successful in choosing the healthier foods.

In line with previous reports on subjective value computation, the vmPFC as well as other brain regions represented an overall stimulus value for the chosen food and the difference between the chosen and not chosen foods (see Methods and Results for GLM-FV in Appendix B). A brain-wide analysis revealed no differences in the representation of subjective value for stressed and control participants, suggesting that basic mechanisms of value computation remained unchanged. Because the behavioral modeling had indicated that the taste might have driven choices more strongly in stressed participants compared to controls, I subsequently assessed the influences of health and taste on the BOLD signal in a second GLM (GLM-HT in Appendix B). The stress treatment increased the representation of the relative taste value (of the chosen minus the not chosen food) in a region of interest including the striatum and amygdala that was of particular interest because of both its high glucocorticoid receptor density and its prior associations with evaluating rewards. In order to test whether the vmPFC's connectivity patterns differed during tastier choices, I conducted a psychophysiological interaction (PPI) analysis with a seed in the vmPFC region that encoded the overall chosen food value (PPI-T in Appendix B). This revealed increased functional connectivity between the striatum-amygdala region and the ventromedial prefrontal cortex during tastier choices. Taken together, these results point towards a candidate mechanism through which stress might

increase the importance of taste aspects during value computation by increasing reward signals.

Despite this increased taste signaling, all stressed individuals were in principle still able to overcome misleading recommendations and choose the healthier item, overriding a recommendation for the less healthy food (GLM-OR in Appendix B) and their own conflicting taste preferences. During these choices, all participants recruited a network of left dlPFC, frontal pole, dACC, and superior parietal lobule. To assess differential interactions with the vmPFC during self-control choices, I returned to the vmPFC PPI analysis and computed a contrast between healthier choice trials (PPI-H in Appendix B) and tastier choice trials. This contrast revealed decreased functional connectivity between the left dlPFC and the vmPFC in stressed participants. Taken together, these results present a candidate mechanism through which stress might alter the importance of health aspects during value computation by decreasing regulatory signals.

I was also able to dissociate the aspects of the stress reaction that were associated with these two pathways. The increased taste signaling became stronger the more stress hormone (cortisol) the participants released over the course of the experiment, but was not correlated with self-reports of perceived stress. The purported regulatory health signaling showed the opposite pattern: it became weaker as a function of the stress level that participants had perceived during the stress treatment, but was not correlated with the cortisol reaction.

In sum, these results suggest that both increased reward signaling and decreased regulatory signaling after an acute stress experience combine in their effects to alter value computation in favor of short-term rewards.

2.3 Study 3: Heart rate variability as a biomarker for self-control

Background

Self-control has been associated with better physical and psychosocial health and other desirable life outcomes. However, one challenge when investigating self-control is that participants may improve their score in readily administered methods such as questionnaires and experiments by strategic answering, for example by socially desirable reporting or by trying to behave in a way that they

assume the experimenter would like to observe (experimenter-demand effects). Thus, measures that are easy to collect, but less prone to biases in task performance or strategic reporting might help to improve the prediction of self-control performance when combined with other self-control measures.

One such example is the physiological measure of heart rate variability (HRV). HRV describes the property of the heart in vertebrates that the time between successive beats oscillates on the millisecond scale and no two heart beat pairs directly following each other are of exactly the same length (Grossman and Taylor, 2007). Physically or mentally straining tasks may temporarily reduce HRV (Porges and Raskin, 1969), but when measured at resting conditions, HRV appears to distinguish between states of health and disease, such that reduced HRV is linked to disadvantageous outcomes regarding both somatic (Masi et al., 2007) and mental health (Thayer and Brosschot, 2005). HRV has been linked to self-regulation, but has been investigated primarily in the domain of emotion regulation (for an overview see Kreibig (2010)). Initial evidence associates HRV with functions that are relevant to goal-directed self-control, such as persistence (Reynard et al., 2011) and working memory performance (Gianaros et al., 2004; Hansen et al., 2004). Paralleling the findings on emotion regulation, low resting HRV has been associated with less effective self-control, for example in social conduct and behavioral disinhibition (for a review see Beauchaine (2001)). It has also been associated with slower recovery after acute psychological stressors (Weber et al., 2010). Higher resting HRV in turn has been associated with higher scores in a self-control questionnaire (Daly et al., 2014).

I therefore investigated whether the relationship between resting HRV and self-regulation extends to dietary self-control, and whether HRV could be used to improve the prediction of self-control levels. I hypothesized that higher resting HRV should be associated with higher self-control in dietary choice. Second, I explored whether a link between HRV and dietary self-control persists under stress. On the neural level, I hypothesized that individual HRV differences would be reflected in neural processing within a self-control network including the dlPFC and vmPFC.

Methods

Resting heart rate measurements were taken during Study 2 (see Chapter 2.2 and Appendix B) that investigated stress effects on self-control. The sample is thus the same group of men, but two resting heart beat interval datasets were lost due to recording failure, reducing the number of participants included in Study 3 to 49 (27 stress and 22 control group participants).

Participants first rated 180 food items for taste and health. Then 3 minutes of heart beat intervals were recorded during sedentary rest before participants were randomly allocated to the stress or control treatment. After the treatment (see Section 2.2), all participants completed 210 trials of the self-control task described in the Methods in Section 2.2 while BOLD fMRI was taken.

Heart rate variability was calculated in the time domain, and I chose the total heart rate variability (standard deviation over all normal-to-normal intervals, SDNN) as the biomarker to assess. The total HRV is considered the most robust measure of HRV, and reflects all internal or external processes the organism reacted to at a given time. After extracting the full RR recording without any transformations, the baseline recording was preprocessed with the Artiifact toolbox (Version 2.08, 64-bit, Kaufmann et al. (2011)), which identifies artifacts using the algorithm of Berntson and Stowell (1998). Because even single artifacts may distort the calculation of HRV, this algorithm aims at excluding any potential artifacts before computing the criterion for identifying true artifacts. Following the recommendation of Salo and colleagues (2001), artifacts were deleted in order to obtain the best estimate of SDNN. Subsequently, time-domain measures of HRV were calculated using Fast Fourier Transforms (Berntson and Stowell, 1998; Kaufmann et al., 2011) with an interpolation rate of 4 Hz (spline interpolation) and a Hanning window width that matched the total length of the edited recording.

For the basic details on fMRI recording, acquisition, preprocessing and analysis, please see the Methods for Study 2 (Section 2.2 and Appendix B).

Results and Conclusions

In the behavioral data, I observed a positive association between resting HRV and self-control levels that was as strong as the correlation between self-control

levels and a validated psychometric index of restrained eating. Moreover, when combined in a behavioral model, both measures predicted significant and independent portions of variation in the individual self-control levels. The association of higher HRV and better self-control held true in the face of stress, but stress nevertheless impaired self-control in individuals with high HRV.

To investigate changes at the neural level, I calculated one additional generalized linear model specifically for assessing BOLD differences in trials containing a self-control challenge comparing to those that posed no challenge (GLM-CH, see the Methods in Appendix C). I found that higher HRV (but not higher restrained eating) was associated with higher vmPFC activity when participants faced decisions that challenged their self-control compared to those when no self-control challenge was presented. This vmPFC ROI encoded the value of chosen foods. Moreover, individuals with high HRV showed a decreased sensitivity to taste in this vmPFC region during choice. Taken together, this points to a potential neural pathway for down-regulating the temptation from taste attributes that may facilitate self-control. In contrast, I did not observe a significant correlation between HRV levels and BOLD signal in the left dlPFC.

Overall, these results suggest that resting HRV may serve as a biomarker for self-control abilities and improve prediction of self-control levels.

3. General Discussion

3.1 Causal involvement of the dlPFC in self-control

Study 1 (in Appendix A) used cathodal and anodal transcranial direct current stimulation (tDCS) over the left dlPFC in order to probe the causal involvement of the left dlPFC in dietary self-control decisions. Using both polarities allowed me to test whether the hypothesized contributions of dlPFC in biasing decisions towards the use of self-control could not only be diminished, but also enhanced. An enhancement of function would open up room for potential therapeutic interventions in order to improve self-control.

The results of this study were consistent with the hypothesized role of the dlPFC as a facilitator of self-control in goal-directed choice. Cathodal tDCS reduced the ability to use self-control: participants in the cathodal stimulation

group performed worse under stimulation than at the pre-stimulation baseline, while sham tDCS did not change self-control performance. This suggests that the left dlPFC plays indeed a causal role in a network underlying self-control in the dietary choice paradigm. Decreasing neural firing rates in the left dlPFC by cathodal stimulation putatively reduced the processing and/or propagation of information that was to be fed into the decision network by these neurons, and consequently impaired self-control.

Following the recommendations for tDCS experiments by Parkin, Ekhtiari and Walsh (2015), I included a battery of control tasks to ensure that the above described effects were specific to the dietary choice task. The capacities for working memory, impulse inhibition, or delay discounting were not changed by stimulation, and it also did not shift taste and health preferences. This suggests that the effects of anodal and cathodal stimulation may be specific to implementing self-control, and not due to an altered capacity for more basic underlying cognitive functions that may support self-control.

Finding the left dlPFC being causally involved in dietary self-control choices is well in line with a number of studies that reported dlPFC stimulation to reduce food cravings (Fregni et al., 2008b; Goldman et al., 2011; Montenegro et al., 2012; Jauch-Chara et al., 2014; Kekic et al., 2014; Lapenta et al., 2014). My study extends beyond these earlier results by resolving stimulation-induced changes in the choice process per se. Earlier studies had neither asked individuals to actively regulate their cravings nor to follow a self-control goal. More important from a modeling perspective, the setup of these earlier studies only included point measures (amount of calories eaten and craving level) as the primary outcomes that could be assessed, which precludes more elaborate modeling of decision-making.

The enhancement of self-control after anodal stimulation was contingent on the individual expression of a restrained eating trait (measured by the Three Factor Eating Questionnaire). Participants who in their daily life applied most often strategies for reducing caloric intake profited most from anodal stimulation compared to those who relied less strongly on explicit strategies for restricting their food intake. Such state-dependency of anodal effects has been reported earlier (Silvanto et al., 2008; Silvanto and Muggleton, 2008; Silvanto

and Pascual-Leone, 2008; Weigand et al., 2013): The facilitating effect of stimulation may enhance the current preparation or execution of a certain behavior or cognitive process, or may occur due to stronger synaptic connections in the targeted neural network that reflect these neurons have been implied in this behavior or cognitive process more often in the past.

The specificity of tDCS stimulation with regard to localization of the effect and specific effects of polarities is still debated (Batsikadze et al., 2013; Bestmann et al., 2015). While we can assume that stimulation affects the area under the active electrode, current actually flows between this electrode and the reference electrode, and thus potentially affects a wider range of areas between the two poles (Parkin et al., 2015). We may therefore conclude that the stimulation has affected at least the target area, but it might also have changed computations in other areas between the electrodes. In order to pinpoint how exactly stimulation changed computations in the underlying neural circuits, a follow-up study therefore will combine tDCS with concurrent fMRI in order to assess the extent and nature of changes in the decision network that are caused by stimulation. This allows for better assessing the specific impact of the stimulation. Overall, Study 1 presents a proof of principle that self-control cannot only be impaired by decreasing information processing in the left dlPFC, but also enhanced by facilitating neuronal firing and information transmission in this site. In any case, the left dlPFC contribution appears crucial to maintaining self-control in goal-directed choices.

3.2 Stress and self-control

Study 2 (in Appendix B) presents the first evidence that acute stress modulates two pathways in the decision circuitry of the brain that combine in their effects to bias self-control choices in favor of short-term rewards. Regarding my initial questions whether an external modulator would impair self-control by causing an increase in reward signaling, a decrease in regulatory signaling, or both, coherent evidence suggested that in the case of acute stress both of these influences were present. I observed up-regulation of signaling for the short-term taste reward, and down-regulation of signaling about the long-term health goal.

In the choice behavior of stressed participants, I noticed a stronger preference for the immediately rewarding tastier foods. Modeling the behavior revealed that this bias towards choosing the tastier food was increased both by the cortisol reactivity and the perceived stress level of the individuals. While at the level of observed choices both reactions to stress resulted in decisions favoring the instantly rewarding, tastier food, using fMRI allowed me to delineate the influence of both components on the neural level, indicating that the emotional and physiological components of the stress reaction act on separate neural pathways.

Compared to the control group, stressed participants showed a stronger correlation of BOLD activity in the amygdala and ventral striatum with the relative taste value, i.e. the taste value of the chosen compared to the not chosen food option. This may be interpreted as a stronger representation of taste attributes. Moreover, when stressed participants chose the tastier foods, amygdala and ventral striatum showed a stronger positive functional connectivity with the vmPFC than in the control group. This is in line with reports that activity in the ventral striatum is seen when participants choose immediate over delayed rewards (Hariri et al., 2006), and that activity in the amygdala and ventral striatum may influence reward value coding in the vmPFC (Hampton et al., 2007; Rudebeck et al., 2013; Jenison, 2014). The strength of this functional coupling was positively correlated with the cortisol response.

Although the stressed participants prioritized immediate taste rewards in their choices more often than the control group, they were not abandoning the long-term health goal altogether. Stressed participants frequently chose the healthier option. When doing so and successfully overriding the misleading recommendations for tastier, but less healthy foods, both stressed and control participants engaged the left dlPFC and other prefrontal areas, contrary to the intuitive notion that stress might simply reduce prefrontal activation. However, the more participants felt stressed, the less likely they were to follow the health goal when it mattered most, i.e. when health differences were highest. Paralleling this behavioral result, I found that stress, and specifically the emotional component of feeling stressed, impaired the robustness of the modulatory connection between the dlPFC and the vmPFC when participants had to

overcome their own taste preferences in order to choose the healthier option. This might in turn have weakened the down-regulation of the increased taste signals.

Overall, self-control under stress thus may be impaired by a combination of two neural mechanisms that enhance the motivating influence of taste on food choices, and decrease the effectiveness of regulatory signals in favor of a health context.

3.3 Resting HRV as a predictor of variation in self-control levels

Study 3 (in Appendix C) investigated the potential of resting heart rate variability (HRV) as a physiological marker of self-control. Such a marker would be a useful addition to other tools of investigation if it reliably explained variance in self-control behavior that is not explained by other self-control measures such as psychometric questionnaires or behavioral tasks.

Both HRV and self-control can be described as the outcome of integration processes. HRV is co-determined by the nervous and cardiopulmonary system and represents the extent to which behavioral and metabolic demands can successfully be integrated (Grossman and Taylor, 2007). Self-control relies on integrating and potentially re-evaluating actions in the context of attaining higher order goals.

In the behavioral data, I observed a positive association between resting HRV and self-control levels. Participants with higher HRV were less affected by taste temptations when they faced choices that challenged their self-control. This was paralleled at the neural level, where participants with higher HRV showed a weaker representation of taste attributes during challenging choices in the ventromedial prefrontal cortex (vmPFC), pointing towards a lower integration of taste in the overall values of the food options. The vmPFC has been associated with calculating subjective values of options during choice (Bartra et al., 2013; Clithero and Rangel, 2014), but also with regulating autonomic responses (Benarroch, 1993). Contrary to my a priori prediction, I did not observe a correlation of HRV with dlPFC activity. Such a link had been reported before for

emotion regulation (Lane et al., 2009), but in contrast to my study, the authors had measured HRV during active regulation.

The resting HRV that was measured with relatively inexpensive and commercially available equipment over only a few minutes predicted self-control in the dietary choice task as well as a validated psychometric index of dietary behavior (the restrained eating scale of the three Factor Eating Questionnaire, RSE). When both HRV and RSE were entered in a joint behavioral model, they both were significantly related to dietary self-control, indicating that both measurements explained different components of the variance in choice. Combining the self-report measure RSE with the biomarker HRV thus gave a more accurate account of future self-control behavior, indicating that HRV could be a useful addition to other measurement tools.

HRV and self-control behavior were reliably associated even when the environmental context changed. Study 2 had shown that experiencing acute stress reduced dietary self-control. The resting HRV that was measured before the stressor onset predicted self-control levels after stress in both the stressed and not stressed participants.

In sum, this suggests that resting HRV may serve as a biomarker of self-control in dietary choice and in combination with questionnaire measures of dietary restraint may improve predicting dietary self-control performance.

3.4 Future directions in the investigation of self-control

It is important to realize that over the course of a lifetime, the successful use of self-control may depend on repeating the self-control behavior over a longer time, and if a lapse occurred, quickly recovering it. Thus further situational and dispositional factors may play a role. Reflecting this thought, the follow-up study of Moffitt and colleagues on the participants of the Marshmallow Test used a compound measure of self-control that was not only based on their test results in the delay of gratification paradigm, but additionally included reports on impulsive aggression, hyperactivity, lack of persistence, inattention and impulsivity that gave a more complete picture of how the children conducted themselves outside the laboratory situation at several time points. When a task

requires repeating a behavior often enough to achieve a certain outcome (e.g. exercise or doing schoolwork (Duckworth et al., 2007; Galla et al., 2014)), self-control is associated with *discipline*, and it may require *persistence* in taking up the successful behavior again after a failure (Bhanji and Delgado, 2014). Capturing these mechanisms will potentially require a combination of laboratory tasks and other assessment tools, and assessing component measures of self-control at several time points during a longitudinal study.

Self-control often requires the ability to *delay gratification* (Mischel et al., 1989): Is a person willing to wait to obtain an outcome in the future, or does she prefer a less valuable outcome that is available now (e.g. in an inter-temporal choice task)? While early work conceptualized this ability to delay gratification as a pure trait variable, it became increasingly clear that the situation and how inter-temporal choice problems were presented contributed to the observed behaviors: Being able to delay the consumption of reward may also hinge on believing that a future outcome will arrive at all if another person needs to deliver it (Andreoni and Sprenger, 2012, 2015; Epper and Fehr-Duda, 2015), will arrive within a specific time period (McGuire and Kable, 2013), that the environment is sufficiently predictable so that it makes sense to assume the outcome can also be consumed later (Lahav et al., 2011), or also that one's own abilities will suffice to actually reach the outcome. Thus in delay of gratification it plays a role how self-control tasks are framed in laboratory studies, but also which beliefs an individual has formed in the environment that she regularly encounters.

Whether delay discounting shows more trait- or state-like characteristics is still debated (for a discussion see the review by Story et al. (2014)). Open questions are for example: Does discounting in one domain generalize to other domains, as some authors suggested (Odum, 2011; Bickel et al., 2012)? For instance it has been suggested that when predicting health behaviors, the prognostic quality of monetary discounting paradigms is not satisfactory (Story et al., 2014). Therefore the field must still work to determine which experimental paradigms or which combination of experimental and observational measures could be used to predict the propensity to invest in one's own health. Of particular practical interest would be a measure that allows assessing the

progress in self-control after interventions. Another related question is: To which degree is discounting behavior heritable (MacKillop, 2013) versus a function of environment, and how could childcare and education help children understand that forgoing immediate pleasure can pay large dividends in the future?

4. General Conclusions

Self-control is a key skill that has important implications for life success. However, humans express this capacity to a highly variable degree, and behavioral studies have indicated that individuals show considerable changes in their self-control behavior depending on situational context. In order to better understand interactions between individual decision-making and challenging situational factors, I turned to studying the effects of one environmental factor, stress, on neural systems that most likely underlie planning and generating the individual behavioral differences we observe. One specific mechanism, a circuit between the dorsolateral and ventromedial prefrontal cortex (dlPFC and vmPFC) has been suggested to be important to self-control as it may provide information about a goal while evaluating choice options and thereby bias choices in favor of self-control (Hare et al., 2009; Hare et al., 2011a; Harris et al., 2013; Hare et al., 2014; Rudorf and Hare, 2014). This is in line with the more general notion that the dlPFC might bias neural processing in favor of a current goal context (Miller and Cohen, 2001).

Concerning the question whether and how the dlPFC might bias value computation during goal-directed choice in order to support self-control, my studies provide four key pieces of evidence that are in line with the notion that the dlPFC might introduce or stabilize a bias in favor of a current goal. First, the tDCS study in Appendix 1 showed that impeding the neural processing in dlPFC by cathodal stimulation decreased the effective use of self-control in order to follow a health goal. Second, it showed that facilitating information processing and propagation by anodal stimulation interacted with existing strategies to restrain food intake and may increase self-control in those individuals who are

regularly applying such strategies. Taken together, this suggests that the dlPFC is causally involved in goal-directed self-control choices.

Regarding the question of how the use of self-control might be changed by environmental challenges, the stress study in Appendix B delivered further key pieces of evidence. This study showed that self-control under stress might be compromised by a combination of increased signaling of immediately accessible reward and a decreased regulatory signaling in favor of the long-term goal of choosing healthy foods. Particularly interesting in this regard was the fact that this decrease in regulatory dlPFC-vmPFC coupling for self-control choices was more pronounced the more individuals had consciously perceived themselves to be stressed. In sum, the results also call upon future research to continue investigating multi-regional interactions that may combine in their effects, but also to include both physiological and affective aspects of the stress reaction in models of self-control because these factors may influence separate parts of the choice mechanism.

Lastly, I explored possible improvements in predicting an individual's future use of dietary self-control use of an individual by combining behavioral with physiological measures that are less prone to reporting bias. The results from study 3 suggested that resting heart rate variability (HRV) may serve as a biomarker for self-control abilities and improve prediction of self-control levels.

Overall, the findings of these studies bear implications for our understanding of self-control in other health-related domains. For example, stress-induced impairments of self-control may contribute to aggravating addictive behaviors (Tang et al., 2015) and other conditions such as major depression and bipolar disorder (Arnsten, 2009; McEwen et al., 2015). A better understanding of the neural circuits underlying successful self-control behavior may help to better target and test interventions that help individuals maintain control in challenging environments.

Eventually, addressing these mechanisms might not only help individuals to realize goals they once decided were worthwhile pursuing, but might more broadly enable them to express abilities that can only be honed by constantly working on them over time.

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List of Abbreviations

ACC – anterior cingulate cortex
BA – Brodmann area (cytoarchitectonic areas after Korbinian Brodmann)
BMI – body mass index
BOLD – blood oxygen level dependent
CAN – central autonomic network
CPT – Cold Pressor Test
dACC – dorsal anterior cingulate cortex
dlPFC – dorsolateral prefrontal cortex
ECG – electrocardiogram
fMRI – functional magnetic resonance imaging
FWE – family-wise error (correction)
GLM – generalized linear model
HPA axis – hypothalamic-pituitary adrenal axis
HR – heart rate
HRV – heart rate variability
ITC – inter-temporal choice
lPFC – lateral prefrontal cortex
mA – milliampere
MAD – median absolute deviation
MNI – (coordinate space of the) Montreal Neurological Institute
mOFC – medial orbitofrontal cortex
NN interval – normal-to-normal interval, between two R-peaks in the ECG
OFC – orbitofrontal cortex
PET – positron emission tomography
PFC – prefrontal cortex
PPI – psychophysiological interaction
PSL – perceived stress level
rCBF – regional cerebral blood flow
ROI – region of interest
RR interval – interval between two R-peaks of the ECG curve (also NN interval)
RSE – restrained eating scale of the TFEQ
RT – reaction time
rTMS - repetitive transcranial magnetic stimulation
SAM axis - sympathetic-adrenal medullary axis
SD – standard deviation
SDNN – standard deviation of normal-to-normal intervals (total HRV)
SECPT – Socially Evaluated Cold Pressor Test
SEM – standard error of the mean
SSRT – stop-signal reaction time
SVC – small-volume corrected
tDCS – transcranial direct current stimulation
TFCE – threshold-free cluster enhancement
TFEQ – Three Factor Eating Questionnaire
TMS – transcranial magnetic stimulation
VAS – visual analog scale
vmPFC – ventromedial prefrontal cortex
WM – working memory

Appendix

A. Appendix to Study 1

Changing left dlPFC excitability with tDCS modulates dietary self-control

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Abstract

The left dorsolateral prefrontal cortex (dlPFC) has been suggested to support self-control in goal-directed decision-making. Yet whether it is causally involved in the calculation of subjective stimulus values within a neural network underlying self-control decisions is still unresolved. We performed a transcranial direct current stimulation (tDCS) study with cathodal, anodal, and sham stimulation over the left dlPFC in order to test its causal role in self-control. Specifically, we tested decisions that pit immediate taste rewards against long-term health goals in a dietary choice task. We found that cathodal stimulation increased the self-control failure rate, while anodal stimulation selectively improved self-control in participants with a higher tendency to cognitively restrain their food intake. Our results are consistent with the theory that engagement of the left dlPFC supports self-control success in goal-based choices.

Introduction

Self-regulation is a critical aspect of successful decision-making. A wide range of positive life outcomes have been linked to higher self-control, from higher socio-economic status to better mental and physical health (Mischel et al., 1989; Duckworth, 2011; Moffitt et al., 2011; Schlam et al., 2013). Neuroimaging studies have identified the dorsolateral prefrontal cortex (dlPFC) as a key correlate of self-control in goal-directed decisions in which multiple stimulus attributes have to be considered in order to select the ultimately superior option from a choice set (Hare et al., 2009; Hare et al., 2011a; Hare et al., 2011b; Hare et al., 2014; Foerde et al., 2015). Yet the actual causal function of the left dlPFC in goal-directed self-control decisions is still unclear.

In order to test the dlPFC's causal involvement in biasing choices towards a health goal context, we conducted a transcranial direct current stimulation (tDCS)

experiment, in which we stimulated the left dlPFC with negative (cathodal) or positive (anodal) current, as well as a sham stimulation control. Generally, tDCS is thought to modulate the membrane potential, i.e., the excitability of the underlying neural tissue. With positive, anodal stimulation, neurons under the electrode are brought slightly closer to depolarization, so firing is putatively promoted, whereas negative, cathodal tDCS makes depolarization of the neural membrane harder and thus decreases firing rates (Purpura and McMurtry, 1965; Liebetanz et al., 2002). However, it has been noted that the net effect of the stimulation may depend on the nature of neuronal populations under the electrode, i.e., how excitatory and inhibitory neural networks are affected (Parkin et al., 2015) and which underlying cognitive functions the task taps into (Tremblay et al., 2014).

We define self-control as forgoing a tempting, immediate reward in order to achieve an outcome that ultimately yields a greater benefit. In the case of food choice, this means foregoing a tasty, less healthy food option that would yield an instant taste reward, in favor of a healthier, yet less tasty alternative that helps to achieve the long-term goal of staying healthy. Earlier neuroimaging studies have suggested that the dlPFC is involved in delay of gratification or self-control (McClure et al., 2004a; McClure et al., 2007; Hare et al., 2009; Figner et al., 2010) and down-regulating cravings (Kober et al., 2010). Figner and colleagues used transcranial magnetic stimulation (TMS) to temporarily inhibit activity in a similar left dlPFC region and showed that this results in a bias towards immediate rewards in an inter-temporal choice task, suggesting a role for dlPFC in temporal discounting. Potentially contradicting these results, Hecht, Walsh & Lavidor (2013) also observed more impatient inter-temporal choices under the putatively facilitating effect of anodal tDCS on the left dlPFC, however this result was obtained using a bifrontal montage with the cathode placed over the right dlPFC, which induces a confound because the impairments in self-control could also be caused by reduced activity in right dlPFC. Moreover, a profound concern about the monetary inter-temporal choice task is that its measurement of the discount factor can be confounded by risk perception (Andreoni and Sprenger, 2012; Epper and Fehr-Duda, 2015). Risk preferences might change the choice function regardless of the participant's patience if she worries that the delayed outcome might not arrive and therefore prefers immediate payment.

Thus, the exact role of the dlPFC within the neural networks that serve self-control is still unresolved. Based on earlier work from our group (Hare et al., 2009; Hare et al., 2010; Hare et al., 2014), we hypothesized that dlPFC modulates the calculation of a subjective stimulus value in the vmPFC (Kable and Glimcher, 2007; Tom et al., 2007; Ballard and Knutson, 2009; Boorman et al., 2009; Hare et al., 2009; Basten et al., 2010; Hare et al., 2010; Kahnt et al., 2010; Plassmann et al., 2010; Shenhav and Greene, 2010; Hare et al., 2011a). We assume that this modulation either strengthens the importance of long-term benefits (e.g., health) during the value computation process such that they yield a higher stimulus value for the healthier option in the calculation than the immediately gratifying option (i.e., eating the tastier food), or that the modulation down-regulates the focus on short-term benefits (i.e., taste), or both. Behaviorally, all of these options result in a bias towards choosing the ultimately superior reward over the immediate gratification.

Although the evidence for a causal role of left dlPFC in self-control is still inconclusive, a substantial number of noninvasive brain stimulation studies in humans have established a causal role of the dlPFC in other higher-order cognitive functions that may also be recruited in self-control. These include: working memory, emotion regulation, risk taking, planning, semantic processing, categorization, and attention, yet the nature of the dlPFC's contribution to these processes has not been fully specified (for a recent meta-analysis see Tremblay et al. (2014)). Moreover, the findings are mixed with regard to specific contributions of the left and right hemisphere, and in some functions, similar effects have been reported for different stimulation polarities with the same montage.

Working memory is a core function for supporting goal-based self-control, when individuals need to keep their goal in mind. Most tDCS studies with an electrode montage where the anode was placed on the left dlPFC and the cathode over a reference site (but not on the right dlPFC; see Tremblay et al. (2014)), found increased working memory performance (Fregni et al., 2005; Ohn et al., 2008; Andrews et al., 2011; Mulquiney et al., 2011; Teo et al., 2011; Zaehle et al., 2011; Gladwin et al., 2012; Jeon and Han, 2012; Meiron and Lavidor, 2013; Vanderhasselt et al., 2013). However, the findings regarding cathodal stimulation are less consistent. Mylius and colleagues (2012) reported that cathodal stimulation over

the left dlPFC benefited working memory, while in contrast the same cathodal stimulation montage decreased working memory performance in the study of Zaehle et al. (2011). Similarly unclear results were found for the related function of planning, which was improved by both cathodal and anodal stimulation over the left dlPFC (Dockery et al., 2009).

The finding that inhibitory dlPFC stimulation reduces cravings for consuming a variety of substances including: food, nicotine, alcohol and other drugs, is more robust and consistent than the effects on working memory. Stimulating the dlPFC with tDCS may help to curb cravings: a recent meta-analysis by Jansen and colleagues (2013) found a medium effect size for both rTMS and tDCS in reducing cravings for substances of abuse and food. Stimulation with direct current was shown to reduce cravings for alcohol (Boggio et al., 2008; den Uyl et al., 2015), nicotine (Fregni et al., 2008a; Fecteau et al., 2014) and methamphetamine (Shahbabaie et al., 2014) and induced quicker characterization of valence attributes in an implicit association test with words related to alcohol (den Uyl et al., 2015). Applying high-frequency rTMS on the left dlPFC similarly curbed cravings for nicotine (Eichhammer et al., 2003; Amiaz et al., 2009; Li et al., 2013; Pripfl et al., 2014) and food (Uher et al., 2005; Van den Eynde et al., 2010), and Camprodon, Martinez-Raga, Alonso-Alonso, Shih & Pascual-Leone (2007) found high-frequency rTMS on the right dlPFC to reduce cocaine craving in dependent individuals.

Another study provided more direct evidence for a modulatory role of the dlPFC in valuation: Camus and colleagues (2009) showed that low-frequency rTMS over the right dlPFC decreases the value assigned to food items. This might indicate that missing dlPFC input to the vmPFC leads to a smaller valuation signal. It is important to note that the effect of inhibitory stimulation over the dlPFC might depend on the stimulation site: stimulus values have been found to be encoded in different parts of the dlPFC, and following a gradient of functions in the lateral PFC (Koechlin et al., 2003), more anterior areas of the dlPFC might participate in valuation, while posterior areas might serve as links between valuation and motor control systems in order to guide the selection and execution of suitable actions (Basten et al., 2010; Hare et al., 2011b).

Beneficial effects on cravings have been reported for various configurations of anodal dlPFC stimulation. Jansen and colleagues (2013) concluded in their meta-analysis that it is equally effective to stimulate the left or the right dlPFC, despite the lateralized dlPFC involvement that is routinely found in fMRI studies on self-regulation. We hypothesized that anodal tDCS will facilitate the use of self-control by modulating stimulus value computations in favor of a health goal, while applying cathodal tDCS will lead to computations that favor taste and thus result in lower levels of self-control. Indeed, we found that cathodal tDCS decreased self-control levels compared to sham stimulation. Furthermore, we found that the beneficial effect of anodal stimulation on self-control was greater in individuals with a greater propensity to restrain their eating behavior in everyday life.

Methods

Participants

The Ethics Committee of the Canton of Zurich approved the study protocol and all participants provided written informed consent at the day of the study. Several participants' data were excluded from analysis because they failed to meet *a priori* defined inclusion criteria or to pass initial data quality checks conducted before any comparisons of the stimulation groups were made. The study asked for written compliance with a health goal for the time of the experiment (see below). 6 men (no women) indicated they would not comply with the health goal, and thus their data were excluded from any analysis. Note that these participants still completed the experimental procedures and received the same compensation through food and monetary incentives as those who agreed to comply with the goal to eat healthy. In other words, there was no incentive for the participants to lie about following the health goal. One additional male participant had to be excluded because the necessary choice set could not be constructed for him due to the fact that he reported only the most extreme values on all health and taste ratings. Data from 3 participants (2 male) had to be excluded because they confused the response keys or repeatedly forgot the identity of the reference item. Lastly, data from one female participant were excluded because she never used self-control in the baseline condition, precluding any inferences about within-subject changes due to stimulation. This left 45 men (Median 24 years ± 2.14 MAD)

and 45 women (Median 23 years ± 2.2 MAD) in the final dataset. No participants reported any history of acute or chronic psychiatric or somatic conditions. Participants were pre-screened in telephone interviews to ensure they did not suffer from any allergies, food intolerances, or eating disorders. To ensure that the snacks in our food choice task would be a temptation to participants, participants were only eligible if they reported regularly consuming snack foods (at a minimum 2-3 times per week), while at the same time trying to maintain an overall balanced and healthy diet.

Participants were randomly allocated to stimulation conditions. The anodal (30 participants, 15 female), cathodal (29 participants, 16 female), and sham (31 participants, 14 female) stimulation groups did not differ from each other with regard to age, body mass index (BMI), or eating habits (as assessed by the Three Factor Eating Questionnaire) (see Table 1). They also did not differ with regard to impulse control (as assessed by the stop signal reaction time, SSRT), working memory capacity (assessed as forward digit span), or inter-temporal choice behavior before stimulation, nor did they differ in the hunger feeling that they reported before the choice task (see Table 2).

tDCS stimulation protocol

The active electrode (5 x 7 cm) was placed on the left dlPFC (see Figure 1a). The reference electrode (10 x 10 cm) was placed over the vertex, slightly off-centered to the contralateral side. The active electrode was placed so that it covered the two coordinates depicted in Figure 1b. These coordinates were selected from overlapping fMRI regions of interest (ROIs) for self-control success > failure in previous fMRI studies (Hare et al., 2009; Maier et al., 2015) with MNI peaks at [-46 18 24] and [-30 42 24]. The coordinates for both dlPFC and vertex were identified in each participant using a neuronavigation system (see insert in Figure 1b). We applied anodal, cathodal or sham tDCS over the left dlPFC using a commercially available multi-channel stimulator (neuroConn GmbH). Between a ramp-up and ramp-down phase of 20 seconds, active stimulation with 1 milliampere (mA) took place for 30 minutes (anodal and cathodal group) or 5 seconds (sham). Sham stimulation was either delivered with positive or negative

current, counterbalanced over the whole sham group. Participants were blind to the stimulation condition.

Procedure

Participants rated 180 food items for health and taste. Food items were shown as color photographs on the computer screen. Before or after these ratings, participants completed a battery of control tasks that were performed both pre- and post-stimulation: a stop signal reaction time task (SSRT), a self-paced digit span working memory (WM) test, and a self-paced monetary inter-temporal choice task (ITC). In order to exclude stimulation effects on taste and health ratings, participants also re-rated a subset of items after the stimulation for both taste and health. All tasks were run in a randomized order.

After all pre-stimulation tasks had been completed, we asked participants to sign a health goal statement, in which they indicated whether they would commit to maintaining a health goal during the following food choice task or not. The statement read: "In this study, we want to investigate how people make healthy food choices. Therefore we ask you to maintain the goal of eating as healthy as possible during this study. Specifically, we ask you to try and choose the healthier of the two food options on each trial. However, these are real decisions, and you are required to eat the food that you chose in one randomly selected trial. We realize this may be more difficult for some people than others, and it is important for us to know whether you agree to this goal or not. Your participation and payment are not contingent on your response. However, this is important for the scientific validity of our study, so please mark your answer below honestly. Please mark "yes" if you agree to do your best to follow the health goal. Please mark "no" if you do not want to commit yourself to the health goal." Participants could mark below whether or not they would commit to this goal, dated and signed the document and handed it back to the experimenter. After everyone had signed the contract and had indicated their current hunger feeling, all participants made 60 food choices that would serve as a baseline for within-subject comparisons of self-control level before and during stimulation. Subsequently we calibrated the stimulator and initialized a 3-minute stabilization period, in which current flowed, but participants were not yet allowed to start on the subsequent food choice task

under stimulation. All food choices were made under stimulation, and randomization of the post-stimulation control tasks ensured that all tasks had an equal chance of being run in the remaining 5-10 minutes of the stimulation time. Once they had finished all post-stimulation control tasks, participants completed a battery of questionnaires (Three Factor Eating Questionnaire (TFEQ), Cognitive Reflection Test (CRT), "Big Five" (NEO-FFI), socio-economic status) and indicated whether and how much they had tried to comply with the health goal throughout the study, whether tDCS had been felt, and whether participants had any problems understanding or following the instructions (manipulation check). 30 minutes after they had made their final choices, participants received and ate their selected food.

Self-control paradigm

In the self-control food choice paradigm, participants chose which food they wanted to eat at the end of the study. In order to reach their health goal, they should choose the healthier item as often as they could. However, the paradigm was engineered such that health and taste dimensions between the food options always conflicted. Participants knew that one of their choices would be realized in the end, and they would have to eat whatever they chose on the trial that was randomly drawn for being paid out. In order to motivate food choice, participants had been asked eat a small snack 3 hours prior to the study and consume nothing but water in the meantime. All choices in the self-control paradigm were individually engineered for each participant from their taste and health ratings in order to create tempting food choice pairs. In type A choice blocks, participants chose between a strictly healthier and less tasty alternative that differed by at least one percentile on both the health and taste dimension from the tastier, less healthy items that were presented onscreen in each of the 10 trials (see Figure 2). In order to comply with the health goal, participants would have to say "no" to the item on the screen in this trial type. In type B choice blocks, a strictly tastier and less healthy item served as the alternative for the block, which required participants to say "yes" to the less tasty, more healthy items presented onscreen during the 10 choice trials in that block in order to comply with the health goal. The order of type A and B blocks was pseudo-randomized and counterbalanced across participants.

In both block types, the alternative food was displayed for 3 seconds before the start of the block. During each choice trial, participants had 3 seconds to make their choices, and each decision was separated by a jittered inter-trial interval of 2-6 seconds. To further incentivize choice, participants were instructed that one of the two alternative foods on a given trial selected for realization would be randomly paid out if they did not respond within the maximum of 3 seconds. To assess a within-subject change in self-control, participants made 60 choices (6 blocks) before stimulation and 120 choices (12 blocks) under stimulation.

Health, taste, and hunger ratings

Participants were instructed to rate taste regardless of the healthiness and vice versa for each of our 180 food items on a continuous slider scale on the screen that showed visual anchor points from -5 ("not at all") to +5 ("very much"). The same scale was used for the hunger rating, which participants provided at the beginning of the food choice task.

Stop signal reaction time task

We used a standard stop-signal-reaction time task (Logan and Cowan, 1984; Logan et al., 1984; Cubillo et al., 2010; Cubillo et al., 2014) in order to assess whether inhibitory control would be compromised by our stimulation. In the SSRT task, participants had to press a button as quickly as they could whenever a figure appeared on the screen ("go task"), but had to stop the initiated movement if another figure appeared above the first with a few milliseconds delay ("stop signal"). The initial delay between the stop signal and the go signal was 0.25 seconds, and task was adaptive, adding 0.05 seconds delay to the next inhibition trial whenever the participant's rate of successful movement inhibition was greater than 50% of the inhibition trials (adding up to a delay of maximum 0.95 seconds), and subtracting 0.05 seconds whenever the participant's success rate in inhibiting the button press fell below 50%. Stimuli were presented on the screen with a jittered duration between 0.5 and 1.25 seconds, and late responses that were given after the stimulus had disappeared from the screen were not counted. Trials with (25) and without stop signal (75) were randomly mixed in the run.

This measure could be calculated only for a subset of the total group because several participants either pre- or post-stimulation adopted a strategy of waiting for the stop signal to appear before they decided whether to try pressing the key (indicated by negative stop signal reaction times, calculated by subtracting the average presented delays from the average reaction times). We compared data from 22 Anodal, 20 Cathodal and 21 Sham participants out of our group of 63 participants who showed a positive stop signal reaction time and thus did not employ a waiting strategy.

Digit span task

In order to control for possible changes in working memory capacity, participants completed a computerized digit span task according to the procedure of Wechsler (1997). The screen would first show a series of 5 numbers, each for 1 second, and then prompt the participant to enter the numbers as she remembered them. If the participant entered a correct sequence in ascending ("forward") order two times in a row, the difficulty level increased by one digit (up to a maximum of 12 digits). If the participant failed two times in a row, or alternated between correct and incorrect answers more than seven times without reaching two sequential corrects, the task stopped and prompted participants to enter the digits in descending ("backward") order in the following trials. Again participants needed two corrects to reach the next level, stopped at 12 digits, or if they reached the failure criteria described above. Here we report only forward digit span scores, because we discovered during data collection that the computerized task allowed for participants to "cheat" and enter the backwards order responses in the forward direction by simply starting to input their responses from the right hand side of the screen. We excluded data for two participants from these analyses. For one participant in the Sham group, data for the post-stimulation control were lost due to a computer crash. One participant in the Anodal group was detected to cheat by writing down all sequences on his instruction sheet.

Inter-temporal choice task

To control for possible effects on discounting behavior, we ran an inter-temporal choice (ITC) task based on the paradigm of Cooper, Kable, Kim &

Zauberman (2013). Participants were instructed that they earned a part of their total payment in this task (60 CHF were paid as a baseline on the day of the study, and the present discounted value of 40 CHF from the ITC was paid at the time specified by the participant), and we would randomly draw from the runs before or after the stimulation session in order to realize one trial. In Cooper and colleagues' version of the ITC task, participants have to bid an amount between 1 and 40 CHF in a BDM auction (Becker et al., 1964) in order to be paid CHF 40 after a variable delay. Whenever they bid more than a randomly determined counter offer between 0 and 40 CHF, they receive the delayed payment of 40 CHF in the indicated number of days. Whenever they bid less than the counter offer, they receive the amount of the counter offer at the day of the study. When their bid equals the counter offer, a coin flip decides whether they will receive the delayed or immediate payment. This mechanism ensures that it is in the participant's best interest to bid their true value for the equivalent of 40 CHF. We downscaled the delays from Cooper and colleagues, choosing 14 linearly spaced delays ranging from 13 to 181 days from the day of the experiment.

We calculated a discounting score for each participant as the area under the curve for all bids, where higher bids indicate a longer willingness to wait for the delayed outcome. We only report data from N = 68 participants (24 Anodal, 18 Cathodal, and 26 from the Sham group) who showed a consistent pattern of discounting, excluding data from participants who showed erratic choice behavior (i.e., valuing the delayed outcome higher than the immediate outcome, or showing inconsistent discounting for subsequent time points).

Statistical Analyses

All analyses were performed with Matlab (Release 2014b, version 8.4.0.150421, The MathWorks Inc. (2014)) or R (Version 3.2.1 , "R Core Team" (2015)) statistical software packages.

Reaction times

We also investigated reaction times as a function of self-control failure in the model as specified below.

Log RT = SCF * condition * stimulation * RSE + abs Tdiff + abs Hdiff + BMI

As the distribution of reaction times was non-normal, we applied a natural logarithm and fit a linear mixed effects model optimizing parameter estimates by restricted maximum likelihood. T-tests use the Satterthwaite approximations to degrees of freedom.

Results

Control tasks

We found no effects of tDCS stimulation over left dlPFC on working memory, response inhibition, or monetary temporal discounting (Table 2). Furthermore, the stimulation did not change the taste or health ratings for the food items (Table 3). Because the distribution of hunger levels was skewed, we assessed differences by a Kruskal-Wallis nonparametric one-way ANOVA and report median and median absolute deviation (MAD) as percentages of maximum hunger level. The level of hunger did not differ between the stimulation groups ($Median_{Sham}$ = 80.1 ± 11.1 %, $Median_{Anodal}$ = 80.5 ± 12.7%, $Median_{Cathodal}$ = 79.3 ± 11.5%; X^2 (2,87) = 0.15, p = 0.93).

Self-control behavior

We modeled self-control failure (SCF; defined as choosing the tastier, less healthy item) in a mixed-effects binomial regression that estimated possible interactions between trial-level (absolute taste and health differences between the alternative and the current onscreen option, and a dummy regressor in which ones denoted choices under stimulation and zeros choices in the baseline condition), and participant-level variables (stimulation condition, restrained eating score (RSE)), while controlling for BMI. The model included random intercepts and slopes for the subject-level effects and the effect of taste and health differences to capture the individual increase in self-control failure rates within participants.

SCF = condition * stimulation * RSE + abs Tdiff + abs Hdiff + BMI

The results of this regression showed that, at baseline, neither the cathodal ($z = -1.25$, $p = 0.21$) nor anodal ($z = -0.64$, $p = 0.53$) stimulation groups differed significantly from the sham group in their self-control performance. We report all estimated coefficients along with their standard error of the mean (SEM) in Table 4. The model also shows that in the pre-stimulation baseline, higher taste differences generally increased self-control failure ($z = 6.53$, $p = 6.5e-11$), whereas high health differences decreased self-control failure ($z = -11.05$, $p < 2e-16$). Lastly, higher restrained eating scores were associated with reduced self-control failure during baseline choices ($z = -3.03$, $p = 0.002$).

During the active stimulation condition, we found that left dlPFC stimulation differentially influenced self-control behavior as a function of polarity. Cathodal stimulation resulted in decreased self-control compared to sham stimulation ($z = 2.27$, $p = 0.02$; see Figure 3). Moreover, while we did not observe a main effect of anodal stimulation, there was an interaction with restrained eating characteristics. High-restrained eaters in the anodal group showed a greater improvement in self-control under stimulation relative to the cathodal group ($z = 2.8$, $p = 0.009$; Figure 4).

Reaction times

Reaction times under stimulation were faster than baseline for all groups ($T = -8.36$, $p < 2e-16$), most likely reflecting learning or practice effects on the task. Greater taste differences at baseline resulted in overall slower reactions when self-control was successful ($T = 4.6$, $p = 7.04e-06$), while greater health differences sped up reaction time during successful self-control ($T = -4.32$, $p = 2.84e-05$). This pattern was reversed in self-control failure trials, in which greater taste differences were associated with quicker reactions ($T = -4.07$, $p = 4.88e-05$) and greater health differences with slower answers (beta = 0.07 ±0.01, $T = 5.98$, $p = 2.35e-09$). Participants with a higher cognitive restraint score reacted more quickly in self-control success trials (beta = -0.09 ± 0.04, $T = -2.47$, $p = 0.02$), and tended to react more slowly when they failed to use self-control (beta = 0.037 ± 0.02, $T = 1.75$, $p = 0.08$). However, there were no significant main effects or interactions with stimulation polarity on reaction times (see Table 5).

Discussion

Consistent with the dlPFC's hypothesized role in facilitating self-control during goal-directed choice, inhibitory, cathodal tDCS over the left dlPFC impaired self-control ability. Specifically, cathodal participants performed worse under stimulation relative to the pre-stimulation baseline, whereas sham stimulation did not change self-control performance (see Figure 3). This indicates that the left dlPFC is causally involved in a network that supports self-control behavior. Suppressing neuronal populations in this region, and thereby reducing the propagation of the information these neurons convey, reduces the effective use of self-control.

Based on our control tasks that assessed the participants' capacities for working memory, impulse inhibition, and discounting in inter-temporal monetary choices, we did not find any differential effects of stimulation polarity on other cognitive functions that may relate to self-control. Stimulation polarity also did not lead to shifts in taste or health preferences. Thus, the changes in self-control observed under cathodal and anodal stimulation over left dlPFC appear to be specific to the execution of self-control and not an alteration in a more basic underlying cognitive function supporting self-control.

Both choice outcome and reaction time analyses suggest that participants incorporated health into their decision processes in the pre-stimulation baseline trials. At the level of choice outcomes, greater differences in health led to more frequent use of self-control. Moreover, self-controlled choices were made more rapidly when there was a higher difference in health between the two options. In contrast, self-control failures had longer latencies if the difference in health was greater.

Our results are well in line with a number of studies that found dlPFC stimulation to reduce cravings for specific foods (Fregni et al., 2008b; Goldman et al., 2011; Montenegro et al., 2012; Jauch-Chara et al., 2014; Kekic et al., 2014; Lapenta et al., 2014), and three of these five studies (Fregni et al., 2008b; Jauch-Chara et al., 2014; Lapenta et al., 2014) also reported a reduced caloric intake after dlPFC stimulation. However, it still remains unclear from these findings how the reported effects on craving translate into self-control choices, as none of the

previous studies consider the choice process, but just its outcome. Another important distinction between these studies and ours is that none of the previous work instructed participants to follow a self-control goal or actively regulate their cravings during the study. Moreover, all of these studies used a montage with the anodal electrode over the right dlPFC (except Fregni, Orsati and colleagues, who additionally tested anodal stimulation on the left dlPFC and found a similar, although slightly weaker effect of left dlPFC stimulation reducing caloric intake, while it did not reduce cravings) in order to test the "right-brain hypothesis for obesity" by Alonso-Alonso & Pascual-Leone (2007). Potential laterality differences as a function of self-control context remain an important open question, but the current evidence suggests that anodal stimulation to either hemisphere may yield beneficial effects.

In line with the previous findings of Kekic and coworkers (2014) on food cravings, we observed the effect of anodal stimulation to depend on the individual expression of a restrained eating trait. Facilitating effects of anodal stimulation may be state-dependent (Silvanto et al., 2008; Silvanto and Muggleton, 2008; Silvanto and Pascual-Leone, 2008; Weigand et al., 2013), i.e., they may depend on the cognitive functions that underlie a behavior that is currently prepared or executed (Andrews et al., 2011; Heeren et al., 2015), or on the strength of synaptic connections in the targeted circuit that reflect prior engagement of these neurons in executing behavior (Silvanto et al., 2008). The effects of anodal stimulation might help stabilize neural connectivity during the active use of certain behavioral strategies: We observed that participants who scored higher on the restrained eating scale in the Three Factor Eating Questionnaire (TFEQ, Stunkard & Messick (1985)) were more successful in self-control under anodal stimulation (see Figures 4a and 4b), possibly because the stimulation enabled them to better use their existing neural pathways or strategies for restraining the intake of less healthy foods.

Although combined into a trait measure, the strategies that the restrained eating scale of the TFEQ measures are not necessarily habitual: they include diverse strategies such as: counting calories and taking smaller helpings of food, excluding particular foods from one's diet, eating more slowly to feel satiety earlier, and eating less for specific period of time after having broken a diet. While

excluding certain foods or taking smaller helpings might be instances of habitual control (Rangel et al., 2008), i.e., it is possible to assign a value to these actions based on earlier experience, practices such as counting calories and eating less after breaking one's diet require constant updating and comparison to the current state of the diet to assign a value to the action of choosing one of the food options, which can only be achieved by a goal-directed valuation system.

The differential impact of stimulation on high-restrained eaters in the anodal and cathodal groups indicates that their self-control success relies on the function of the left dlPFC. Under stimulation, highly restrained eaters in the cathodal group were not able to use their behavioral strategies as effectively to avoid self-control failure, while highly restrained eaters in the anodal group were more effective. The aforementioned results of Kekic and colleagues showed that anodal tDCS on the left dlPFC reduced craving most effectively in participants who were more reflective in their food choice behavior. Mirroring our findings in the inter-temporal choice control task, Kekic and colleagues also observed no changes in temporal discounting behavior due to stimulation.

Together, these findings suggest that anodal stimulation might have enhanced behavioral tendencies that were already present – in this case, being more reflective during food choices. Thus, the facilitation by anodal stimulation may represent an interaction between stimulation and the ongoing cognitive/neural context. For example, anodal tDCS applied during the performance of an n-back task led to better performance on a subsequent retest than anodal tDCS delivered without concurrent execution of the n-back task or sham tDCS (Andrews et al., 2011). Similarly, in an emotional self-regulation task in which anxious individuals try to modify their prevalent bias of attending towards negative stimuli in the environment, Heeren et al. (2015) have shown that when delivered together with attention bias modification (a behavioral intervention that biases attention away from threats), anodal stimulation decreased negative attention bias (i.e., how long threatening stimuli are fixated) more effectively than applying the attention modification method together with sham tDCS or without any stimulation.

Assuming that anodal stimulation may have tapped into the existing behavioral strategies of highly restrained eaters, we are still left with the question

of what the precise mechanistic contribution of the dlPFC is to this behavior. Notably, a larger proportion of the strategies for restraining food intake measured in the TFEQ require an individual to track whether a planned behavior meets a goal (e.g., when counting calories, a dieter always has to track whether a food still fits into the overall daily calorie budget), a strategy that may involve comparing the decision options in order to assess how closely they match a health goal, or somehow strengthening the importance of that goal during the value computation process. Therefore, stimulation of left dlPFC may alter the degree to which stimulus attributes are weighted or compared with respect to a current behavioral goal. Importantly, neither anodal nor cathodal stimulation changed how much participants liked the taste of the food items or their opinions on healthiness when they did not have to make a choice (i.e., taste and health ratings remained stable before and after stimulation). Thus the stimulation effect must result from a change during the choice process. From the current dataset, we can only conclude that the dlPFC indeed has a role in biasing the decision process towards healthier choices, but we cannot directly address whether this bias comes from modulating a value computation or comparison process, or both.

Thus, while there is substantial evidence that both anodal and cathodal dlPFC stimulation alter aspects of cognition and motivation that could influence self-control, we do not yet understand how exactly such stimulation changes computations in the underlying neural networks. In order to precisely determine the dlPFC's exact role, we would need more insight into other nodes of the computational circuit at the same time, for example by collecting concurrent fMRI at the time of tDCS stimulation. This would allow mapping both where changes in processing happen at the time of choice due to stimulation and how they changed the flow of information between the nodes. Our study provides a proof of principle that stimulation induces changes in self-control but is only a first step towards examining more closely how connectivity between the nodes of the self-control network changes as a result of stimulation. Future research should address this question, for example by using parallel fMRI-tDCS.

Conclusion

Cathodal tDCS on the left dlPFC diminished self-control levels compared to sham stimulation. The effect for anodal tDCS depended on the expression of a restrained eating behavior trait in the individual. The type of stimulation differentially modulated the self-control promoting effects of restrained eating strategies: While cathodal stimulation uniformly decreased self-control regardless of a restrained eating trait, anodal stimulation facilitated self-control more in high-restrained eaters. Our findings provide support for a model of dietary self-control in which the dlPFC is causally involved in biasing choices in favor of a long-term health goal. Further work is needed to disentangle at which stage in the choice process (calculation or comparison of subjective choice values) this bias is introduced.

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Author contributions

S.U.M., T.A.H. and C.C.R. designed research with input from A.R.B.; S.U.M. and A.R.B. performed research; S.U.M., A.R.B. and T.A.H. analyzed data; S.U.M. wrote the paper with input from T.A.H., A.R.B. and C.C.R. Stars and double stars denote shared first and last authorship.

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Tables

Table 1. Participant demographics

	M S	*MAD S*	*M A*	*MAD A*	*M C*	*MAD C*	X^2	*p*
Age	23	2	23.5	2.3	23	2.3	1.29	0.53
BMI	21.5	2.3	22.1	2	21	2.1	0.84	0.66
TFEQ-R	10	1.6	10	1.8	10	2.1	1.11	0.58
TFEQ-D	8	2	8	1.8	8	1.8	0.47	0.79
TFEQ-H	6	1.8	6	1.7	6	1.8	1.25	0.53

Distributions for all demographic variables were non-normal for all groups (A = Anodal, C = Cathodal, S = Sham). Therefore we report Median (M) and Median Absolute Deviation (MAD) and assess between-group differences with a non-parametric Kruskal-Wallis one-way ANOVA (degrees of freedom between groups = 2, degrees of freedom within groups = 87).

BMI = Body Mass Index

TFEQ-R = Cognitive restraint of eating score of the Three-Factor Eating Questionnaire (maximum score on the scale = 21)
TFEQ-D = Disinhibition of restrained eating score of the Three-Factor Eating Questionnaire (maximum score on the scale = 16)
TFEQ-H = Hunger susceptibility score of the Three-Factor Eating Questionnaire (maximum score on the scale = 14)

Table 2. Control measures

	M S	*MAD S*	*M A*	*MAD A*	*M C*	*MAD C*	X^2	*df(1)*	*df(2)*	*p*
SSRT pre	0.24	0.05	0.23	0.08	0.21	0.08	0.68	2	60	0.71
SSRT post	0.22	0.04	0.23	0.07	0.2	0.06	1.19	2	60	0.55
WM pre	7	0.7	7	1.11	7	0.94	1.39	2	85	0.5
WM post	8	0.89	8	1.11	7	0.78	5.03	2	85	0.08
ITC pre	5376	1110	5626	1122	4924	1001	1.86	2	65	0.39
ITC post	5444	1107	5658	1055	4657	1087	2.99	2	65	0.22

Before and after stimulation, the following control measures were collected:

SSRT = Stop-Signal Reaction Time test
WM = Working memory (forward digit span)
ITC = (monetary) inter-temporal choice task

For all stimulation groups, Median (M) and Median Absolute Deviation (MAD) are listed as measures were non-normally distributed. Between-group differences were assessed with a non-parametric Kruskal-Wallis one-way ANOVA (df (1) = degrees of freedom between groups, df (2) = degrees of freedom within groups).

Figures

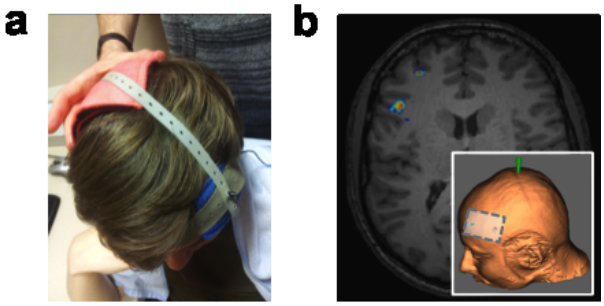

Figure 1. Montage of the tDCS electrodes. Panel **(a)**: The active electrode was placed on the left dlPFC, with the reference electrode slightly off-centered to the contralateral side over the vertex. The stimulation site was localized individually with BrainSight based on structural MRI scans. The dlPFC coordinates for stimulation depicted in panel **(b)** were derived from overlapping ROIs for self-control success > failure in the fMRI studies of Hare et al. (2009) and Maier et al. (2015) using a similar dietary self-control paradigm. As depicted in the insert in panel (b), the active electrode was placed to cover the two coordinates (MNI peaks at [-46 18 24] and [-30 42 24]).

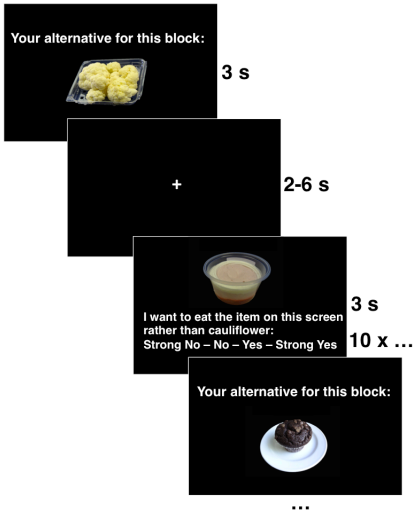

Figure 2. Dietary self-control paradigm. Participants made 60 choices in a baseline condition and 120 choices under stimulation, with a maximum decision time of 3 seconds and a jittered inter-trial interval of 2-6 seconds. Choice options were presented in blocks of 10 trials, with a reference item ("alternative") presented before each block. Blocks alternated between a healthier, but less tasty reference item (type A, first screen), and a tastier, but less healthy reference item (type B, last screen). Participants responded on a 4-point scale (strong no – strong yes) whether they wanted to receive the item presented within the block or the alternative.

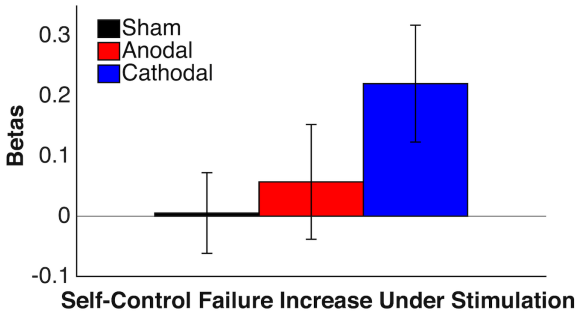

Figure 3. Main effect of stimulation. Cathodal stimulation led to a significant increase in self-control failures compared to the individual baseline without stimulation.

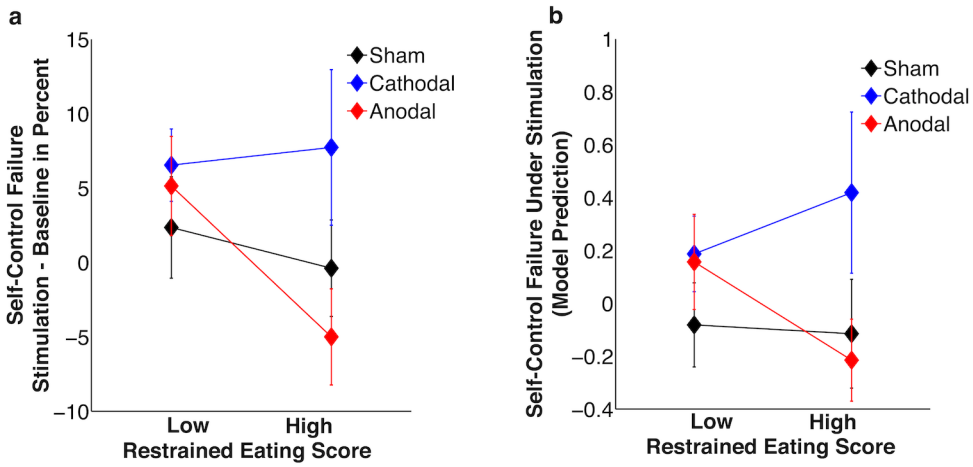

Figure 4. Comparison of raw data and modeled estimates of self-control failure in participants with high and low restrained eating scores. Panel **(a)** depicts the percentage change in self-control failure at the time of stimulation compared to the individual participant's baseline (subtracting the baseline from the stimulation score). The scores are aggregated in mean values for the sham, anodal, and cathodal groups. We divided the dataset by a median split based on the participants' restrained eating score from the TFEQ to visualize differential stimulation effects for high (right) and low (left) restrained eaters: Participants with the highest restraint scores profited most from stimulation. Panel **(b)** depicts the prediction of our behavioral self-control model for the same data.

B. Appendix to Study 2

Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits

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Abstract

Important decisions are often made under stressful circumstances that might compromise self-regulatory behavior. Yet the neural mechanisms by which stress influences self-control choices are unclear. We investigated these mechanisms in human participants who faced self-control dilemmas over food rewards while undergoing fMRI following stress. We found that stress increased the influence of immediately rewarding taste attributes on choice and reduced self-control. This choice pattern was accompanied by increased functional connectivity between ventromedial prefrontal cortex (vmPFC) and amygdala and striatal regions encoding tastiness. Furthermore, stress was associated with reduced connectivity between the vmPFC and dorsolateral prefrontal cortex regions linked to self-control success. Notably, alterations in connectivity pathways could be dissociated by their differential relationships with cortisol and perceived stress. Our results indicate that stress may compromise self-control decisions by both enhancing the impact of immediately rewarding attributes and reducing the efficacy of regions promoting behaviors that are consistent with long-term goals.

Introduction

Choices between the temptation of immediate gratification and better long-term outcomes are a frequent occurrence in daily life. The ability to forgo an immediate or salient reward in order to achieve another goal (i.e. self-control) has been linked to a person's physical, social, and economic well being (Duckworth, 2011; Moffitt et al., 2011). Given the importance of self-control abilities in many facets of life, recent studies have begun to examine the neurobiology of self-control (Crockett et al., 2013; Hare et al., 2009; Hare et al., 2014; Kable and Glimcher, 2007; Luo et al., 2012; McClure et al., 2004; van den Bos et al., 2014), but thus far, these investigations have generally examined self-control choices in carefully controlled settings designed to minimize participant discomfort or stress. In reality, however, many important decisions are made during or immediately following stressful events that occur regularly in daily life (Smyth et al., 1998). Experimental data demonstrate that stress can have both immediate and long-lasting effects on brain and behavior (Duckworth et al., 2012; Kandasamy et al., 2014; Lewis et al., 2014; McEwen and Morrison, 2013; Schwabe and Wolf, 2010). Even relatively moderate and acute stressors have been shown to affect decision-making (Gathmann et al., 2014; Lempert et al., 2012; Porcelli and Delgado, 2009; Porcelli et al., 2012; Schwabe et al., 2012; Schwabe and Wolf, 2009; Starcke et al., 2008). However, the neurobiological effects of stress on the important class of choices involving temptation and self-control remain unknown. Here, we examined the impact of acute stress on brain activity during self-control choices over primary food rewards and show that it caused multiple changes in the brain's decision circuitry that can be linked to either cortisol levels or the perception of being stressed.

Previous studies on the neuroendocrine and behavioral consequences of stress suggest that acute stress could affect choices requiring self-control in at least two ways. Stress has been claimed to impair prefrontal functions such as directing attention and inhibiting inappropriate actions, which would be fundamental for goal-based control of actions and self-control (Arnsten, 2009; Starcke and Brand, 2012). At the same time, stress has been reported to amplify "craving" or "wanting" signals that might bias an individual towards choosing immediately rewarding options (Adam and Epel, 2007; Pruessner et al., 2004; Sinha et al., 1999). Therefore, we hypothesized that acute stress would impair self-

controlled decisions in favor of actions leading to salient and proximal rewards through one or a combination of these two mechanisms.

To test this hypothesis, we combined an acute stress manipulation with a self-control decision paradigm and investigated the neural mechanisms underlying the predicted stress-induced focus on immediately rewarding options. Specifically, we used a previously established self-control task involving binary choices between primary food rewards that varied on the attributes of healthiness and taste (Hare et al., 2009) in combination with the Socially Evaluated Cold Pressor Test (Schwabe et al., 2008) as a means of stress induction (Figure 1 and Experimental Procedures). Using multi-attribute food stimuli allowed us to disentangle the brain's reaction to long-term benefits, such as pursuing a goal of eating healthy, and short-term rewards, for example the pleasurable taste experienced immediately upon eating the food. In addition to the stimuli themselves, we added a choice recommendation on a subset of trials to test how such external information might interact with acute stress to affect self-control. We told participants that the recommended items would be the healthier option in most trials, but that sometimes the recommendation would mislead them towards the less healthy food and, in such cases, they should override the recommendation to maintain their health goal. Consistent with our hypothesis, we found that stressed participants' choices were more affected by short-term taste rewards, and that they encoded taste more strongly in portions of the amygdalae (Amyg) and ventral striatum (vStr). Furthermore, the stress manipulation increased task-dependent connectivity between these limbic regions and a portion of the ventromedial prefrontal cortex (vmPFC) that represented integrated stimulus value. This increased connectivity between vmPFC and Amyg and Str was more strongly correlated with salivary cortisol levels, an indicator of the hypothalamic-pituitary-adrenal (HPA) axis stress response, than with self-reported ratings of stress. In addition, increased stress levels were also associated with decreased connectivity between vmPFC and dorsolateral prefrontal cortex (dlPFC) regions that were activated when engaging self-control. However, in this case the changes in vmPFC-dlPFC connectivity were more strongly associated with self-reports of perceived stress level than salivary cortisol. Thus, these two alterations in task-dependent functional connectivity within the decision network are differentially

related to the HPA axis responses and psychological perceptions following acute stress. Together these findings demonstrate that acute stress induction results in parallel, and at least partially dissociable, alterations to neural decision circuits incorporating both appetitive motivation and behavioral regulation that may combine to impair the brain's ability to exercise self-control in the face of temptations.

Results

Stress manipulation

We recruited individuals who reported making an effort to maintain a healthy lifestyle in terms of diet and exercise, but who still enjoyed and often consumed junk food and thus often faced a self-control challenge in our choice task (see Supplemental Experimental Procedures). These participants were randomly assigned to undergo the stress induction or control procedure before the decision task. Participants in the Stress group reported higher perceived stress levels (PSL) on a visual analog scale (anchors: 0, "not at all" and 100, "extremely") immediately after the SECPT stress induction procedure than those reported in the Control group following the control procedure ($Z = 2.03$, one tailed $p = .02$; see Figure 2A). The Stress and Control groups did not differ significantly on any other mood ratings, but the Stress group reported lower hunger levels (see Table 1 and Supplemental Experimental Procedures). Including hunger level as a control did not change any of the differences in choice behavior described below. In addition to self-report measures of experienced stress, we analyzed salivary cortisol concentrations as an indicator of the activity in the HPA axis following our acute stress manipulation. Figure 2B shows that the stress induction procedure resulted in higher maximum cortisol levels ($Z = 2.19$, one tailed $p = 0.01$) and total cortisol responses (area under the curve (AUC): $Z = 1.87$, one tailed $p = 0.03$) than our control procedure. Furthermore, participants in the Stress group maintained an elevated cortisol level compared to baseline ($Z = 2.18$, one tailed $p = .02$) until the end of the behavioral task (+45 minutes). Lastly, the correlation between individual participant's PSL and AUC cortisol levels was positive, but not significant ($r = 0.17$, $p = 0.26$).

Behavior

Food consumption decisions were based more strongly on the tastiness of each option for participants in the Stressed compared to Control groups. On every trial, participants selected one of two food items (i.e. left or right) to potentially eat following the fMRI scan (see Fig. 1 and Experimental Procedures). A logistic regression analysis testing the influence of health, taste, and recommendations on the probability of choosing the item on the left side of the screen demonstrated that, although healthiness had the strongest overall influence on choice in both groups, (Figure 2C), Stressed participants put a higher weight on the taste of the food items (taste left (i.e. chosen) $t_{49} = 2.13$, $p = 0.04$; taste right (i.e. non-chosen) $t_{49} = -2.30$, $p = 0.03$) than Controls. However, this analysis of choices across all trials does not distinguish between decisions in which health and taste attributes are aligned and trials in which the tastier item is less healthy.

To examine the effects of acute stress on self-control behavior more directly, we tested the probability of self-control failure (choosing a more tasty, less healthy item) in the subset of trials where health and taste attributes were in conflict because the healthier item was less tasty. The participants' decisions on this subset of self-control challenge trials were correlated with their reports of restricted eating behavior in every-day life, such that those with more restricted eating habits made more frequent self-control choices during the task ($r = 0.30$, $p = 0.03$). To compare choice behavior on these trials between the Stress and Control groups, we computed a generalized linear mixed-effects model including regressors for the absolute differences between the chosen and non-chosen food items in health (H_{diff}) and taste (T_{diff}), the recommendations on each trial and the interactions of H_{diff}, $T_{diff,}$ and recommendation with group. Consistent with the analysis over all trials, this regression demonstrated that greater differences in taste between the two options resulted in more self-control failures for stressed participants compared to controls (Fig. 3A; $Z = 4.53$, $p = 6.05e\text{-}06$), with the Stress group failing 24% more often than controls on trials with the most extreme differences in taste. In addition, there were main effects of H_{diff} ($Z = -13.87$, $p < 2e\text{-}16$), T_{diff} ($Z = 6.96$, $p = 3.5e\text{-}12$), and recommendation ($Z = -10.12$, $p < 2e\text{-}16$) across both groups.

Next, we examined how individual differences in cortisol and perceived stress levels related to choice by extending the regression model above to include cortisol (measured as total AUC) and PSL as well as their interactions with all other factors (see Experimental Procedures and Table S1A). This extended analysis again revealed main effects of H_{diff} (Z = -11.09, p < 2e-16), T_{diff} (Z = 5.74, p = 9.34e-9), and healthy recommendations (Z = -7.39, p = 1.49e-13) across all participants, as well as an interaction between Stress group and T_{diff} (Z = 4.23, p = 2.38e-05). In addition, there were significant interactions for PSL X H_{diff} (Z = 2.84, p = 0.01), and PSL X healthy recommendations (Z = 2.47, p = 0.01) such that both were less effective in promoting self-control. Moreover, there was a three way interaction between PSL, Stress group, and T_{diff} (Z = 2.40, p = 0.02), such that stressed participants reporting the strongest feelings of stress were most sensitive to taste attributes. Higher levels of cortisol also reduced the degree to which healthy recommendations facilitated self-control (Z = 2.31, p = 0.02) and there was another three way interaction between cortisol, PSL, and T_{diff} (Z = 2.19, p = 0.03), indicating that higher levels of both cortisol and PSL increased the degree to which taste attributes were associated with self-control failures. Thus both individual PSL and cortisol levels explained additional variance in participants' choice behavior beyond the differences linked to the stress induction procedure overall.

We also investigated the effects of stress on choice reaction times (RTs; Table S2, See Supplemental Information for full details). These RT effects were consistent with the choice data in showing a greater impact of taste on behavior (i.e. faster reaction times) in participants with higher PSL and cortisol levels (t = -3.51, p < 0.0004). However, there was also a main effect of self-control failure such that all participants were slower when choosing a tastier, but less healthy option (t = 4.20, p < 0.00003) indicating that these choices were not simply the result of response inhibition failures, which should result in faster reaction times (see also Table S3 for further analyses related to response inhibition).

fMRI

In order to examine how acute stress influenced the brain's decision circuitry, we analyzed BOLD activity measured during the choice task using a series of general linear models.

First, we tested for regions that reflected the value of food items at the time of choice by computing a model (GLM-FV) that included parametric regressors representing the subjective value of the chosen and non-chosen food item on each trial. The subjective value of food items was computed by combining the weighted values for the taste and health of each food. These weights were derived from the logistic regression summarized in Fig. 2C and were determined individually for each participant (see Experimental Procedures for details). We found that vmPFC and several other regions represented the integrated subjective value of the chosen food for both Stressed and Control groups as well as the relative value difference between the chosen and non-chosen options (Table S4; $p < .05$, whole brain FWE corrected). There were no brain regions that significantly differed in their representations of subjective food value between the Stressed and Control participants after correcting for multiple comparisons. Moreover, a post-hoc two-sample t-test revealed no significant difference between groups in the vmPFC ROI used as a seed in subsequent analyses presented below ($t_{49} = -0.80$, $p = 0.42$). These results suggest that acute stress did not fundamentally change the circuits involved in overall subjective value computation that have been reported by numerous studies across a wide range of decision contexts (Bartra et al., 2013; Clithero and Rangel, 2013).

Next, motivated by the behavioral finding that stressed participants' decisions were biased towards the taste of food items, we investigated the representation of relative taste value (taste of chosen item – taste of non-chosen item) in Stressed versus Control participants (see GLM-HT in the Experimental Procedures). We were particularly interested in the vStr and Amyg given that these limbic structures contain high densities of glucocorticoid receptors (GR) (Ahima et al., 1991; Zoli et al., 1990), and play important roles in signaling the salience and motivational value of stimuli (Bartra et al., 2013; Cooper and Knutson, 2008; Everitt et al., 1989; Jenison, 2014; Litt et al., 2011). Consistent with a role in signaling motivational value, the bilateral Amyg and right nucleus accumbens, a substructure of the vStr, reflected the relative taste value of chosen options more strongly in Stressed compared to Control participants (Fig. 3B; $p < 0.05$, small volume corrected (SVC); Table S5). An exploratory whole brain analysis revealed no further differences in relative taste encoding between

Stressed and Control participants in other areas of the brain. Individual PSL and cortisol levels did not explain additional variance in taste related activity within Amyg and vStr beyond the stress induction procedure, however separating participants along a median split for cortisol level yields results that are qualitatively similar to the Stress versus Control group comparison (Fig. S1A).

In addition to testing for local representations of taste value, we examined changes in functional connectivity (psychophysiological interactions (PPI)) when participants chose tastier items. Specifically, we tested whether connectivity with the vmPFC node of the valuation system identified in GLM-FV differed between Stressed and Control participants during choices in which they selected the tastier item, controlling for connectivity during choices for healthier items. We focused on the vmPFC as a seed because of previous work highlighting the central role of this region in goal-directed choice in general (Bartra et al., 2013; Clithero and Rangel, 2013) and specifically during self-regulated choice (Hare et al., 2009; Hare et al., 2014). We found that positive connectivity between vmPFC and portions of our Amyg/vStr region of interest was greater in Stressed versus Control participants when choosing the tastier item (Fig. 4; $p < .05$ SVC). A whole brain analysis revealed that the Stress group showed greater vmPFC connectivity with several brain regions including the Amyg, vStr, and bilateral insula during tastier choices (Table S6; $p < .05$, whole brain FWE corrected). Furthermore, using a multiple regression analysis, we found that the increase in vmPFC connectivity during tastier choices was more strongly correlated with individual cortisol levels compared to self-reported PSL in the striatum and extended amygdala (Fig. 5C-D; Table S7; $p < .05$, whole brain FWE corrected).

The stronger encoding of relative taste value in areas such as Amyg and vStr that signal the motivational value of objects (Miller et al., 2013), together with their greater functional connectivity to vmPFC at the time of a tastier choice, suggests a potential mechanism for increasing the importance of taste in the value computation processes (Hampton et al., 2007; Jenison, 2014; Rudebeck et al., 2013), and subsequently in the observed choices of the stressed participants, especially those with a stronger HPA axis response to the stressor. It may be that acute stress results in enhanced reward salience or stronger “wanting” (Berridge,

1996; Mahler and Berridge, 2011) for more tasty items and that these motivational signals influence decision processes.

Beyond the intrinsic taste and health attributes of each food, choices and RTs in both groups were influenced by the healthy and unhealthy recommendations. In order to further investigate choices representing the strongest self-control challenges, i.e. refusing a recommended tastier and less healthy food, we ran an additional model (GLM-OR) to test for brain areas that were associated with overcoming both misleading recommendations (i.e. inconsistent with the goal of eating healthy) and conflicting taste preferences in order to choose the healthier option. These trials represent the strongest self-control challenges because both taste preferences and recommendations promote the goal-inconsistent option. Recall that despite the enhanced signaling of relative taste value in motivation and reward circuits, participants in the Stress group often still chose the healthier item. Across both Stressed and Control groups, activity in left dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), and the left superior parietal lobule (SPL) was greater when participants successfully overrode a misleading recommendation and chose the healthier, but less tasty option ($p < .05$, whole brain FWE corrected; Table S8). There were no regions whose activity significantly differed between the Stress and Control groups when participants successfully overrode misleading recommendations (but see Table S9).

Next, we repeated our comparison of the relationship between individual differences in PSL and cortisol levels and vmPFC connectivity, but this time when choosing the healthier over the tastier option. To that end, we calculated the difference in connectivity during healthier versus tastier choices over all participants. This subtraction contrast measures increases in connectivity during choices for food items that are healthier, but less tasty than the alternative (i.e. choices that required self-control). Applying the same multiple regression analysis we used for connectivity during tastier choices revealed that the degree of negative connectivity between vmPFC and dlPFC decreased as a function of participants' PSL ratings and was more closely associated with PSL than cortisol levels (Fig. 5A-B; $p < .05$, whole brain FWE corrected; Table S10). Note that this negative connectivity between left dlPFC and vmPFC is consistent with previous reports on

the neural mechanisms of self-control when overcoming taste temptations (Hare et al., 2009). Thus, while vmPFC connectivity with Amyg and vStr during tastier choices was associated with cortisol levels and not PSL, the opposite relationship holds for vmPFC-dlPFC connectivity during healthier choices. This connectivity is correlated with PSL, but not cortisol. The dissociable links to PSL and cortisol suggest that distinct aspects of the acute stress response alter these two pathways in the decision network during self-control choices.

Discussion

Our findings indicate that stress biases the decision process in the brain by altering two pathways: one that might signal information about the stimulus (e.g. taste), and another that has been linked to context and goal maintenance (e.g. choosing healthy food). At the level of observed choices, we found that stressed participants had an increased preference for immediately rewarding stimulus attributes and that this preference increased as a function of individual perceived stress and cortisol levels. The neuroimaging data complement this behavioral finding and show that acute stress induction results in alterations to multiple nodes of a decision-making network that converges to represent the overall value of stimuli in the vmPFC. However, the similar effects of increased PSL and cortisol on decisions can be dissociated at the neural level by their effects on vmPFC-dlPFC and vmPFC-Amyg/vStr functional connectivity, respectively.

Acute stress induction led to a stronger influence of taste attributes on choice that was paralleled by changes in activity and connectivity patterns in Amyg and vStr. Participants in the Stress group showed stronger correlations between the relative tastiness of the chosen option and BOLD activity in the Amyg and vStr compared to Controls. In addition, we observed that the positive coupling of Amyg and vStr with vmPFC was associated with more immediately rewarding, taste-oriented choices, consistent with previous findings showing that activity in vStr is associated with immediate reward selection (Hariri et al., 2006). Moreover, there was a significant positive correlation between higher cortisol levels and increased connectivity between vmPFC and Amyg/vStr when choosing a tastier food, but no relationship between this increased connectivity and PSL. This dissociation

suggests that the HPA axis response to stress can have effects on neural decision circuits that are distinct from those associated with the subjective perception of being stressed. Enhanced positive coupling between vmPFC and Amyg and vStr regions may indicate the propagation of a stronger motivational signal for the tastier item into value computations. However, although previous studies have shown that activity in these areas can influence reward value coding in vmPFC regions (Hampton et al., 2007; Jenison, 2014; Rudebeck et al., 2013) we note that the PPI analyses we conducted do not indicate the direction of signaling between regions or the presence of monosynaptic connections. Overall, these results are consistent with the idea that these Amyg and vStr signals may be linked to the influence of taste on valuation and choice.

In addition to the effects of our acute stress induction on the HPA axis and Amyg and vStr activity, we observed individual differences in the subjective perception of being stressed that correlated with self-control at the behavioral and neural levels. Specifically, we observed that as PSL increased, larger taste differences between options resulted in more self-control failures. Furthermore, participants with higher PSL were less likely to follow the health goal when it mattered most (i.e. when there was a large difference in healthiness) than lower PSL participants. These affects of PSL on behavior were paralleled by differences in connectivity between dlPFC and vmPFC when participants chose healthier over tastier options. In addition to the altered coupling between vmPFC and Amyg/vStr, we identified a second signaling pathway between vmPFC and dlPFC that showed a reduction in negative connectivity for participants with high PSL. Prior work (Hare et al., 2009; Harris et al., 2013) suggests that this dlPFC-vmPFC connection may help to modulate value comparisons and to integrate taste and health attributes in the vmPFC. A weaker modulatory connection with dlPFC might result in less effective down-regulation of the impact of the taste signaling, resulting in a relative weighting for taste attributes in vmPFC that is too high given the health goal. We speculate that decreased modulation from dlPFC in combination with stronger limbic inputs may combine to create the taste influence that we observed to be more pronounced in stressed participants than in controls. This is consistent with our behavioral finding that individuals with higher levels of both perceived stress and cortisol are most likely to fail on difficult (i.e. high taste difference) self-control

trials (PSL X cortisol X T_{diff} interaction) and that PSL and cortisol levels are linked to dlPFC and Amyg/vStr connectivity with vmPFC, respectively. Thus, stressed participants might be less willing to forego a bit of pleasure (taste) in favor of advancing their health goal because they have both a stronger taste signal entering the valuation process in vmPFC, and less effective levels of connectivity between dlPFC and vmPFC compared to control participants.

Although the neurobiological effects of stress on self-control choices over secondary rewards remain unknown, it has been shown that stress affects goal-directed choices over both primary and secondary rewards. The biasing of the valuation system towards immediate rewards we observed following stress may be a means of trying to maintain allostatic balance. It is interesting to consider our results in light of previous findings showing that the consumption of rewarding stimuli (e.g., palatable food) may help down-regulate physiological stress reactions, in both rodents and humans (Adam and Epel, 2007). Such drives may be particularly strong in the context of self-control choices over primary food rewards. However, stress has also been reported to compromise goal-directed contributions to choices over monetary rewards, biasing humans towards habitual actions (Otto et al., 2013; Schwabe and Wolf, 2009; Schwabe and Wolf, 2010; Soares et al., 2012). When viewing cues or anticipating monetary outcomes, stressed individuals show greater activity in reward regions including the amygdala, striatum, and medial prefrontal cortex (Dagher et al., 2009; Kumar et al., 2014), and acute psychosocial stress may increase dopamine levels in the vStr (Pruessner et al., 2004). Stress also alters risk preferences during monetary gambles in humans (Putman et al., 2010; Starcke et al., 2008; van den Bos et al., 2009), and can change the perception and influence of reward at the time of consumption (Lewis et al., 2014; Porcelli et al., 2012; Preston et al., 2007; Putman et al., 2010; Schwabe et al., 2012; Schwabe and Wolf, 2010; Starcke and Brand, 2012). Moreover, stress has been associated with aggravating addiction processes (Ansell et al., 2012; Koob and Le Moal, 2008). A common theme across many studies of acute stress is that it makes the individual more focused on the present situation. A present bias would be sensible given that throughout evolutionary history, stress has generally occurred in situations in which an acute physical or social threat must be managed in order to ensure survival or status in a group. In

such a situation, coping with the stressor and stress reaction should be prioritized. Given a constraint of limited resources, this means that achieving less pressing long-term goals would need to wait until the stressful situation has been resolved.

Stressful events that may alter behavior remain a common occurrence in modern life. Experience sampling studies have shown that stressful events occur frequently in daily-life and even modestly taxing events have a significant impact on HPA activity and self-reported measures of stress (Jacobs et al., 2007; Smyth et al., 1998; Van Eck et al., 1996). The HPA and psychological indicators of stress found in our participants following the SECPT are in line with the levels reported in previous studies of daily-life stress responses. Following the SECPT stress induction, participants reported a mean perceived stress level of 33%, and had a mean salivary cortisol level of approximately 9 nmol/liter 25 minutes after the stressor. These values are in line with ratings and cortisol levels reported by Smyth et al., (1998) who collected reports of recent and anticipated stressors during the standard daily activities of 120 participants over the course of two consecutive days (24 samples per participant in total). These participants reported recent and anticipated stressors (e.g. family issues, personal relationships, financial and work-related problems) on more than 20% of sampled time points. These experiences were rated as 47% of maximum stress and produced cortisol responses of between 8-9 nmol/liter after 25 minutes depending on the number of concurrent stressors reported. These findings show that stressors unrelated to a specific decision occur with ample frequency in daily life, and as we demonstrate, may influence the response to self-control challenges that arise in close proximity to these stressful events.

The individual reaction to stress depends largely on a person's appraisal of the situation as well as their state of physical health (McEwen, 1998). Our results demonstrate that the effects of stress on self-regulatory behavior are driven at least in part by psychological perceptions of stress that can be dissociated from cortisol responses at the neural level, and have potential implications for diseases such as obesity, addiction, and other pathological behaviors exacerbated by stress. The effects of stress can be increased by overconsumption of tobacco, alcohol, and a rich diet, but can be reduced by healthy activities such as exercise (McEwen, 1998). Therefore, stress response and self-control abilities may be coupled in a

feedback loop: healthy dietary choices and exercise may help to regulate the stress response, while past self-control failures (e.g. overeating) may result in stronger present stress responses that again spur the drive to choose less healthy activities. Thus, treatments that promote effective coping strategies may help to prevent the detrimental effects of stress on self-control decisions by reducing perceived stress and its influence on choice behavior. Testing the degree to which the neural mechanisms underlying the impact of stress on self-regulation that we have identified here generalize to specific clinical populations and other healthy cohorts differing in age, sex, education, or other variables associated with stress sensitivity and self-control will be an important avenue for future studies designed to systematically address these factors.

Beyond determining the effects of acute stress on self-control behavior, our data highlight the importance of multiregional interactions in effectively executing self-control. Previous work has shown that activity patterns within and interactions between valuation and control regions are correlated with individual differences in self-control (Boettiger et al., 2007; Hare et al., 2009; Hare et al., 2014). Others have reported that inhibition of putative control regions via transcranial magnetic stimulation leads to behavioral changes in choices that may require self-control (Figner et al., 2010), but have not shown how this affects the network beyond the area of stimulation. Our acute stress manipulation resulted in altered activity patterns in a number of brain regions and demonstrates that self-control in the context of value-based choice is maintained through a careful balance of connectivity within value computation systems and that the disruption of this balance leads to impairments in self-control decisions.

Experimental Procedures

Participants

Fifty-one male individuals participated in the study (21 ± 2 years SD), and all participants provided informed consent as approved by the Research Ethics Committee of the Canton of Zurich. Participation eligibility was assessed in brief telephone interviews by the recruitment team of the UZH Economics Department, and eligibility for the study was checked again at the day of testing with a brief questionnaire on exclusion criteria (see Supplemental Experimental Procedures).

Participants for this study were selectively recruited to ensure the food choices in our task would represent self-control challenges for them and they would respond similarly to the stress induction (see Supplemental Experimental Procedures). Specifically, we recruited individuals who reported making an effort to eat a healthy diet and exercise regularly, but also still enjoyed and frequently consumed relatively unhealthy junk food items. Participants randomly assigned to the Stress and Control groups did not differ in the self-reported typical weekly mean number of times they consumed fruit and vegetables (Stress = 10.3 ± SD of 3.3, Controls = 10.3 ± 3.0), undertook strength or cardiovascular training (Stress = 3.4 ± 2.2, Controls = 3.7 ± 1.9), or ate junk food items (Stress = 7.7 ± 3.6, Controls = 7.6 ± 4.2).

Experiment timeline

Participants spent a total of 3 hours in the lab. They first rated 180 food items for healthiness, tastiness, and their overall appetitive value. Food items were shown as color images on a computer monitor. Participants then completed the SECPT or the control procedure. They were positioned in the scanner directly afterwards and started working on the food choice paradigm at minute 12-17 after stressor onset, allowing for a cortisol peak measurement right after the first fMRI run, and another measurement after the third run, 40-45 minutes after stressor onset. Each run took 7 minutes, thus the peak of the cortisol measurement was reached during the behavioral task, and cortisol values in the Stress group stayed elevated during the whole scan time compared to the Control group. After the scanning session, participants completed a battery of psychometric questionnaires (see Supplemental Experimental Procedures) and the last saliva measurement, after which they received their chosen food, were debriefed, and paid for their participation.

Stress induction

Stress induction and scanning always took place between 14.00 and 17.00 in the afternoon to account for the diurnal rhythm of cortisol. Twenty-nine participants were randomly allocated to the Socially Evaluated Cold Pressor Test (SECPT, (Schwabe et al., 2008)). Participants had to immerse their hand in an ice water

bath (0-4° C) for 3 minutes while being videotaped and monitored by the experimenter. They were instructed not to communicate and were informed the experimenter would indicate when the test was over. Participants were allowed to remove their hand from the water bath any time, but if they did (N=5, see Supplemental Experimental Procedures), they were asked to keep looking into the camera until the 3-minute test time was over and were instructed that they could try re-inserting their hand in the water. In the control condition, 22 participants had to keep their hand in a warm water bath (35-35° C) for 3 minutes while the experimenter was in the room, but did not videotape them.

Choice task

Overall, participants made 210 choices (70 in each run) between two food items that were presented on a screen. Choice screens (3 seconds) were presented with a jittered inter-trial interval of 2-6 seconds. One choice was randomly drawn at the end, and participants had to eat the item they chose in this trial during the 30-minute waiting period. The participants' goal was to choose the healthier of the two items whenever possible, and we reminded them of this goal in between trials with a health symbol in place of the standard fixation cross. In order to test whether an explicitly wrong recommendation (to eat the less healthy item) would affect the behavior of stressed participants, we recommended in 60 trials to choose the less healthy food. In 120 trials, we recommended – in line with the participants' ratings – choosing the healthier item. The remaining 30 trials had no recommendation and served as a baseline. A white frame around the food item indicated our recommendation; when we gave no recommendation, the white frame appeared around the fixation cross (see Fig. 1 and Supplemental Experimental Procedures).

Cortisol, heart rate, and blood pressure measurements

Behavioral pilots with the SECPT indicated that salivary cortisol would peak 20-25 minutes after stressor onset. Therefore, salivary cortisol was collected at minutes +1 after stressor/control offset, and at minutes +25, +45 and +70 after stressor/control onset with a Salivette® swab (Sarstedt, Nümbrecht, Germany), and stored at -20° C until analysis (see Supplemental Experimental Procedures).

Heart rate was measured throughout the stress/control session (a baseline was collected beforehand) with a Polar RS 800CX watch, and throughout the fMRI session with the built-in ECG system of the scanner. Diastolic and systolic blood pressure was recorded directly before and after participants immersed their hand in the water bath. In line with previous reports, blood pressure and pulse did not differ significantly between Stress and Control participants either before or after the SECPT procedure (Schwabe et al., 2008).

Self-report ratings

Immediately after completing the stress/control procedure, participants indicated on a visual analog scale (VAS), their perceived stress level (PSL), how much they felt in control of the situation, and how angry, sad, happy, anxious, and hungry they felt. All rating scales ranged from 0 ("not at all") to 100 ("extremely") (see Supplemental Experimental Procedures).

Behavioral analyses

Logistic regression over all choices

We examined the impact of taste and health attributes as well as recommendations on each participant's choices by computing the following logistic regression:

$$[1]\ CL = \beta_0 + \beta_1 Taste_L + \beta_2 Taste_R + \beta_3 Health_L + \beta_4 Health_R + \beta_5 Rec_L + \beta_5 Rec_R + \varepsilon$$

In which CL is a binary choice vector taking the value of 1 whenever the left option is selected and 0 otherwise, and the subscripts L and R denote the taste, health, and recommendation status of the left and right items, respectively. Recommendation regressors took the value of 1 whenever that food was recommended and 0 otherwise. Taste and health ratings for each participant were measured using a visual analog scale and z-scored within participants. Differences in the regression coefficients between the Stress and Control groups were assessed using two sample t-tests.

Logistic regression for self-control failure

We modeled the probability of self-control failure in a generalized linear mixed effects model fit by maximum likelihood (Laplace approximation) as a function of the binary variable Group (Stress, Control), and continuous variables of PSL and cortisol level at the subject level and the difference in health and taste between both items, and the recommendations at the trial level. The model included all one, two, and three way interactions between subject level variables and the three trial level variables (see Table S1A for full the listing). For clarity we present the model with only trial level variables below.

$$[2]\ SCF = \beta_0 + \beta_1 H_{diff} + \beta_2 T_{diff} + \beta_3 HRec + \varepsilon$$

SCF is a binary vector taking the value of 1 whenever the participant chooses a less healthy, but tastier item (i.e. self-control failure). T_{diff} is the absolute value of the difference in taste ratings between the two foods, and H_{diff} is the absolute value of the difference in health ratings between the two foods. HRec takes the value of 1 whenever the healthier food is recommended, 0 when there is no recommendation, and -1 when the less healthy food is recommended. The subject level variables PSL and cortisol were z-scored across participants. Note that repeating the model with rank-transformed AUC cortisol values yields similar results (see Table S1B).

fMRI models

The details of the fMRI data acquisition and preprocessing are given in the Supplemental Experimental Procedures.

For each fMRI analysis, we computed general linear models at the single subject level with the Statistical Parametric Mapping (SPM8, Update Rev. Nr. 5236; Functional Imaging Laboratory, University College London) software suite in Matlab, and examined the results at the second, group level using non-parametric permutation tests (N = 5000 permutations) with threshold-free cluster enhancement (TFCE) as implemented in the Randomise function from the FMRIB Software Library 5.0 (FSL; FMRIB, Oxford) (Hayasaka and Nichols, 2003; Jenkinson

et al., 2012). All results are reported family-wise error (FWE) corrected and all coordinates are given in MNI space.

GLM-subjective food value (FV)

To examine neural correlates for the subjective value of the chosen food, we constructed a model with regressors identifying three events of interest (GLM-FV): 1) all choices, 2) trials when the recommended item was chosen, 3) trials when the recommended item was not chosen. Two parametric modulators were included with the first regressor for all choices: P1) the subjective value of the chosen item (FVc), P2) the subjective value of the non-chosen food item (FVnc). Food values for the chosen and non-chosen food were computed as a weighted addition of the taste and health attributes with the weights derived from the logistic regression over all choices described above in equation [1]. In this and all other fMRI analyses, the regressors were defined as boxcar functions with duration equal to the reaction time on that trial, and regressors for head motion, cardiac, and respiratory effects were included to account for BOLD signal variability associated with these effects.

We computed first level contrasts for: 1) FVc, and 2) FVc-FVnc. Lastly, we calculated one and two sample permutation tests to identify activity for all participants or to compare the Stress and Control groups on each measure, respectively.

GLM-health, taste value (HT)

In GLM-HT, we examined the effects of health, taste, and recommendations on BOLD activity using a model with regressors identifying five events of interest: 1) all choice onsets, 2) trials in which the healthier food was recommended and chosen, 3) trials in which the healthier food was recommended and not chosen, 4) trials in which the less healthy food was recommended and chosen, 5) trials in which the less healthy food was recommended and not chosen. Four parametric modulators were included with the first regressor for all choices: P1) Health rating for chosen item (Hc), P2) Taste rating for chosen item (Tc), P3) Health rating for non-chosen item (Hnc), P4) Taste rating for non-chosen item (Tnc). These parametric regressors were not orthogonalized with respect to one another.

We computed first level contrasts for: 1) Tc, 2) Tnc, 3) Hc, 4) Hnc, 5) Tc-Tnc, and 6) Hc-Hnc. Next, we computed a two-sample permutation test between the Stress and Control groups comparing the relative taste value (Tc–Tnc) and relative health value (Hc-Hnc) signals and covariate permutation tests to identify effects associated with individual differences in PSL and cortisol levels. In the relative taste value analysis, we corrected for multiple comparisons within an anatomically defined ROI encompassing all voxels with a non-zero probability of belonging to the bilateral amygdalae or nucleus accumbens as defined by the Harvard-Oxford subcortical atlas (Desikan et al., 2006).

GLM-override unhealthy recommendation (OR)

The behavioral analyses showed that both Stressed and Control participants were able to override recommendations for the less healthy item that were incongruent with their health goal. Thus, we expanded the original GLM-FV to include five (as opposed to the original 3) events of interest: 1) all choices, 2) trials in which the healthier food was recommended and chosen, 3) trials in which the healthier food was recommended and not chosen, 4) trials in which the less healthy food was recommended and chosen, 5) trials in which the less healthy food was recommended and not chosen. Regressor 1 was parametrically modulated by P1) the subjective value of the chosen food (FVc), and P2) the subjective value of the non-chosen food (FVnc).

We computed first level contrasts for the difference between choosing the healthier versus the less healthy food following a recommendation for the less healthy food (regressors 5 and 4). Lastly, we calculated one and two sample permutation tests to identify activity for all participants or to compare the Stress and Control groups, respectively.

PPI

In order to investigate whether the effective connectivity of the vmPFC node of the valuation system identified in GLM-FV differed between stressed and control participants during choices in which they selected the tastier item, we ran a psychophysiological interaction analysis (PPI). First, we created a vmPFC timeseries by extracting the first eigenvariate from a 5mm sphere surrounding the

subject-specific peak voxel for the parametric effect of FVc from GLM-FV within a functional vmPFC mask defined by all significant voxels in the analysis over all participants at p = 0.005 uncorrected. Second, we computed the interaction terms between the vmPFC, and 1) PPI-T, a regressor identifying all trials in which the participant chose the tastier item or 2) PPI-H, a regressor identifying all trials in which the participant chose the healthier item. Third, we estimated a PPI GLM including the following regressors: 1) trials when the healthier item was chosen, 2) trials when the tastier item was chosen, 3) the vmPFC seed time course, 4) PPI-H, and 5) PPI-T.

We computed the first level contrasts for PPI-T and PPI-H minus PPI-T. Lastly, we computed two-sample permutation tests to identify significant differences in these contrasts between the Stress versus Control groups and covariate permutation tests to identify PPI effects associated with individual differences in PSL and cortisol levels.

Author contributions

S.U.M and T.A.H. designed research; S.U.M. and A.B.M. performed research; S.U.M., A.B.M. and T.A.H. analyzed data; S.U.M. and T.A.H. wrote the manuscript with input from A.B.M.

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Figures

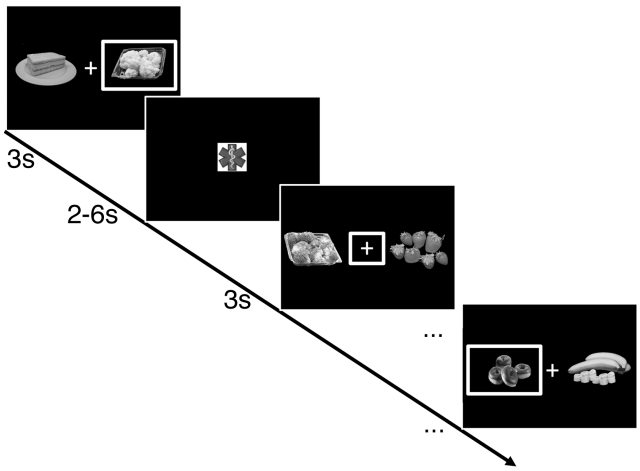

Figure 1. Task structure. Participants had 3 seconds to choose one of two food options on each trial, followed by a 2-6 second jittered inter trial interval in which a health reminder symbol was displayed in the center of the screen. In most trials, the food that the participant had previously rated as being the healthier of the two options was highlighted with a white frame. This white frame represented a choice recommendation to the participant. However, participants knew that in some cases the less healthy item could be highlighted (last depicted trial), in which case they should override the misleading recommendation and choose the healthier item.

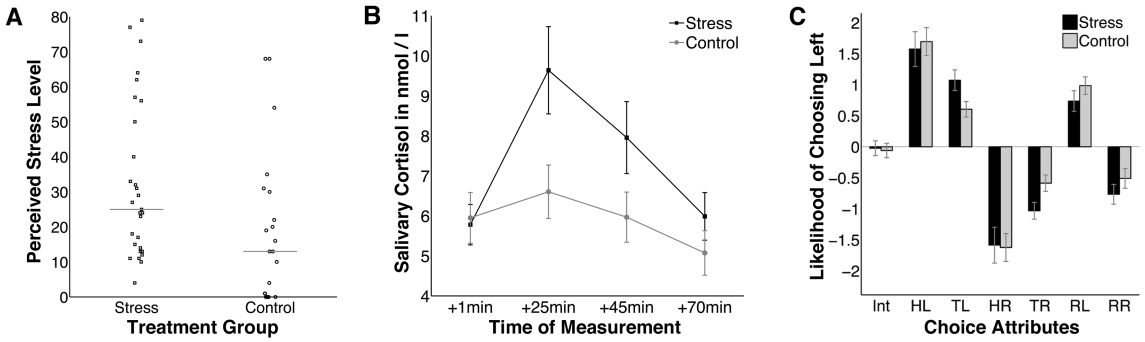

Figure 2. The stress induction procedure changed individual measures of stress and overall choice behavior. Panel (**A**) shows that perceived stress levels differ significantly between the Stress and Control groups ($Z = 2.03$, $p = .02$). Each square or circle represents an individual participant in the Stress or Control group, respectively. The horizontal lines indicate the median for each group. Ratings were made on a scale from 0 ("not at all") to 100 ("extremely") just after the SECPT or control procedure finished. Panel (**B**) shows the average salivary cortisol levels for the Stress and Control groups at baseline (stressor offset +1 minute), peak (stressor onset +25 minutes), directly after the choice task (stressor onset +45 minutes), and at the end of the experiment (stressor onset +70 minutes). Participants in the Stress group had significantly greater area under the curve than Controls ($Z = 1.87$, $p = 0.03$). **C**) The bar graph depicts beta coefficient weights from a logistic regression examining the effects of taste ratings, health ratings, and recommendations for the left and right items on the probability of selecting the left item. The taste of each food had a stronger impact on choice in the Stress compared to the Control group (TL $t_{49} = 2.13$, $p = 0.04$; TR $t_{49} = -2.30$, $p = 0.03$; also see Table S3). All error bars indicate the standard error of the mean (SEM) across participants.

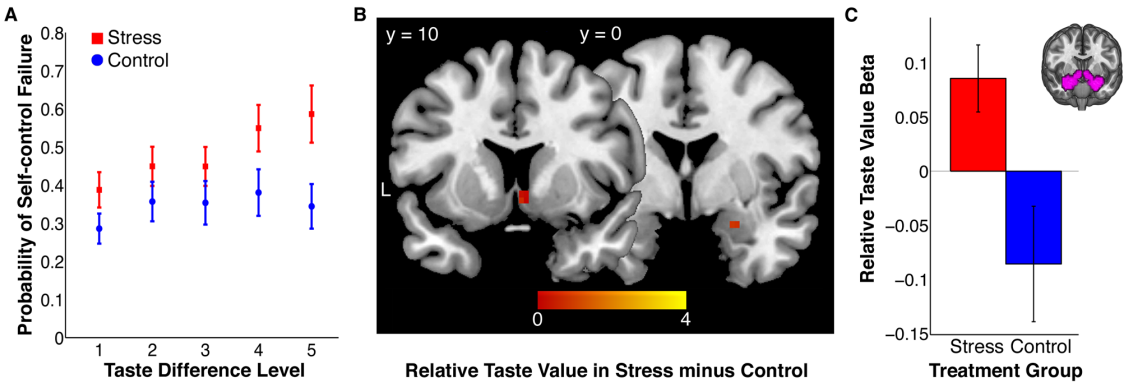

Figure 3. Stress induced differences in the influence of taste on self-control choice behavior and neural activity. **A**) The error bar plot shows the probability of self-control failure for each group as a function of the difference in taste between the two food items (ltaste left – taste rightl). Taste difference values were divided into quintiles to show the increasing probability of self-control failure in the Stress group as taste difference increases (see Tables S1A and S2). **B**) The statistical parametric maps show two regions of the ventral striatum (left) and amygdala (right) where the correlation with relative taste value is higher in the Stress compared to Control group ($p < 0.05$ SVC; see Fig. S1A and Table S5). The color scale represents t-statistics derived from 5000 permutations of the data. **C**) The bar graph shows beta coefficients for relative taste value averaged across all voxels in an anatomical mask of the bilateral nucleus accumbens and amygdala (shown in magenta on the inset brain rendering). The correlation with relative taste value was greater in the Stress compared to the Control group in this anatomically defined ROI ($Z = 2.67$, $p = 0.0069$; see Fig. S1B). All error bars indicate SEM across participants.

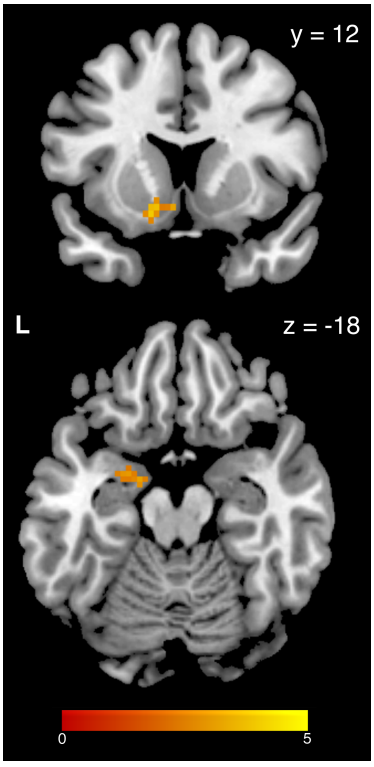

Figure 4. Stress induction resulted in greater functional connectivity between the vmPFC and ventral striatum and amygdala when choosing the tastier food. The statistical parametric map shows areas of the ventral striatum (upper) and amygdala (lower) where the increase in functional connectivity with vmPFC on trials in which the tastier item was chosen is greater for Stress than Control participants ($p < 0.05$ SVC; see Table S6). The color scale represents t-statistics derived from 5000 permutations of the data.

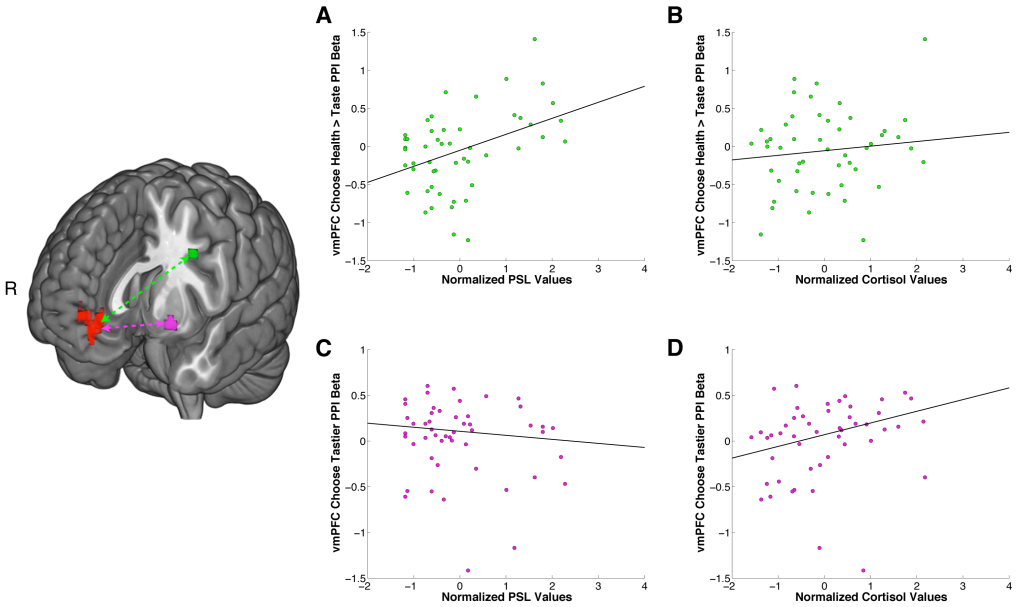

Figure 5. Connectivity between vmPFC and Amyg/vStr and dlPFC are differentially associated with individual differences in PSL and cortisol levels. The brain rendering on the left shows the vmPFC region reflecting the subjective value of food items in red (see Table S4) and regions of the vStr and dlPFC from which the scatter plots in **A-D** are derived in magenta and green, respectively. The magenta voxels in vStr represent the conjunction between voxels showing greater taste choice PPI with vmPFC in the Stress vs Control participants (see Table S6) and those in which taste choice PPI correlates more strongly with cortisol than PSL (see Table S7). The green voxels in dlPFC represent the conjunction between voxels that are more active when using self-control to override taste preferences (see Table S8) and unhealthy recommendations and those in which healthier minus tastier food choice PPI correlates more strongly with PSL than cortisol (see Table S10). Panels **A and B** show scatterplots of dlPFC PPI coefficients with vmPFC for healthier minus tastier food choices against PSL and cortisol levels in green. Panels **C and D** show scatterplots of vStr PPI coefficients with vmPFC for tastier food choices against PSL and cortisol levels in magenta. The black lines in **A-D** indicate robust fits from regressions using iteratively reweighted least squares with a bisquare weighting function.

Supplemental Material for Study 2.

Supplemental Figures

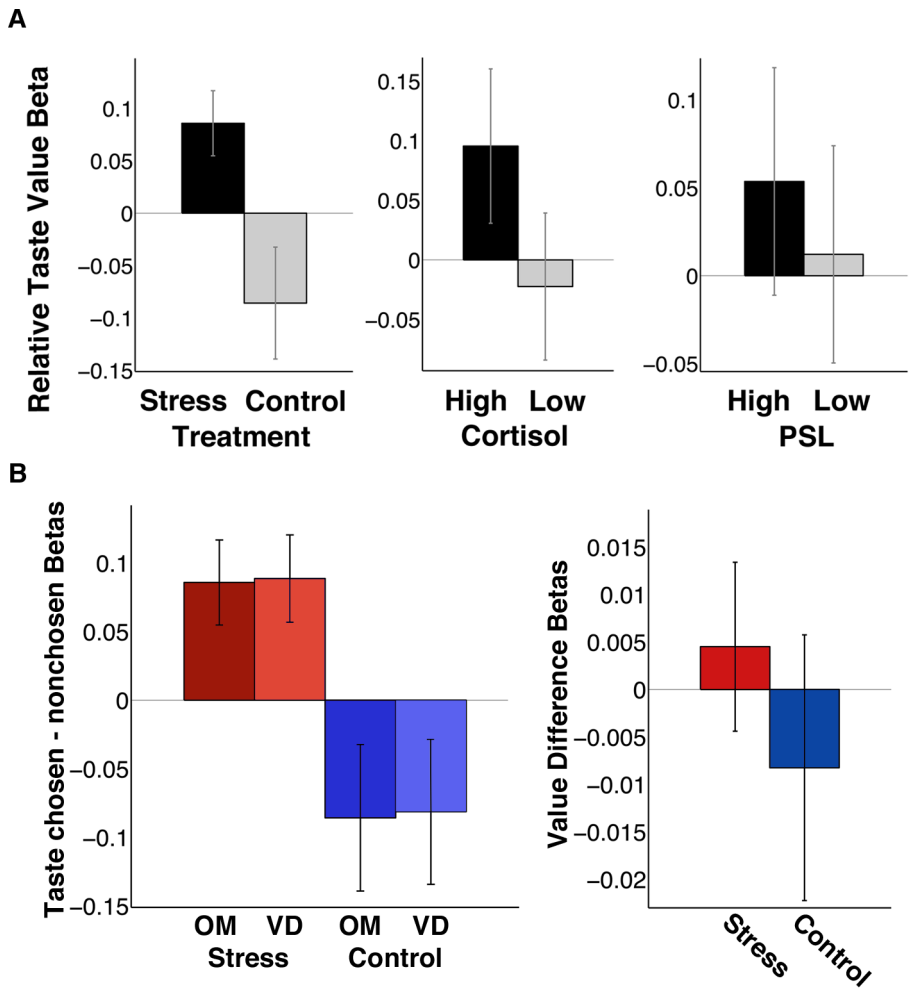

Figure S1, Related to Figure 3. A) Representation of the relative taste value (Taste chosen – nonchosen) in the Amyg/vStr broken down by median splits for cortisol (middle) and Perceived Stress Level (right). For comparison, the left panel shows the relative taste value betas in the Stress and Control groups (Figure 3C in the main text). **B)** The left panel compares the relative taste value betas in the anatomical region of interest that comprises bilateral amygdala and nucleus accumbens from GLM-HT (OM = Original Model) and a version of GLM-HT that additionally accounts for value difference (Value Difference = VD) for both Stress and Control treatment group (see Supplemental Experimental Procedures for GLM-HT-FVdiff). The right panel compares the representation of value difference for both Stress and Control treatment group in the same bilateral amygdala and nucleus accumbens voxels. All error bars denote standard error of the mean (SEM) across participants.

Supplemental Tables

Table S1. Probability of self-control failure by stress treatment group, perceived stress level and cortisol response (Related to Figure 3A).

Regressor	*Estimate*	*Std. Error*	*z value*	*p(z)*
Intercept	-0.15	0.34	-0.44	0.66
Stress group (S)	0.26	0.44	0.58	0.56
Cortisol (CORT)	-0.09	0.37	-0.24	0.81
Perceived Stress Level (PSL)	-0.14	0.33	-0.42	0.68
H_{diff}	**-1.01**	**0.09**	**-11.10**	**< 2e-16**
T_{diff}	**0.43**	**0.08**	**5.75**	**8e-09**
Recommendation (Rec)	**-0.54**	**0.07**	**-7.40**	**1e-13**
S X CORT	0.23	0.44	0.52	0.61
S X PSL	0.04	0.42	0.09	0.93
CORT X PSL	0.02	0.35	0.05	0.96
S X H_{diff}	0.06	0.12	0.53	0.59
CORT X H_{diff}	0.11	0.09	1.18	0.24
PSL X H_{diff}	**0.25**	**0.09**	**2.84**	**0.01**
S X T_{diff}	**0.42**	**0.10**	**4.23**	**0.00002**
CORT X T_{diff}	0.04	0.09	0.46	0.65
PSL X T_{diff}	0.01	0.07	0.12	0.90
S X Rec	-0.14	0.10	-1.50	0.13
CORT X Rec	**0.18**	**0.08**	**2.31**	**0.02**
PSL X Rec	**0.18**	**0.07**	**2.47**	**0.01**
S X CORT X PSL	-0.11	0.42	-0.27	0.79
S X CORT X H_{diff}	-0.20	0.11	-1.85	0.07
S X PSL X H_{diff}	-0.17	0.11	-1.54	0.12
CORT X PSL X H_{diff}	0.08	0.08	0.96	0.34
S X CORT X T_{diff}	-0.14	0.10	-1.36	0.17
S X PSL X T_{diff}	**0.24**	**0.10**	**2.40**	**0.02**
CORT X PSL X T_{diff}	**0.18**	**0.08**	**2.19**	**0.03**
S X CORT X Rec	**-0.22**	**0.09**	**-2.34**	**0.02**
S X PSL X Rec	-0.17	0.09	-1.80	0.07
CORT X PSL X Rec	0.02	0.07	0.27	0.79
S X CORT X PSL X H_{diff}	-0.07	0.10	-0.69	0.49
S X CORT X PSL X T_{diff}	**-0.20**	**0.10**	**-1.93**	**0.05**
S X CORT X PSL X Rec	-0.10	0.09	-1.12	0.26

Estimates are logistic regression coefficients from a mixed-effects generalized linear model fit by maximum likelihood.
H_{diff} is the absolute health difference between both items; T_{diff} is analogously the absolute taste difference between both items.

Recommendation was modeled with the value of 1 for a healthy recommendation, 0 for no recommendation, and -1 for an unhealthy recommendation.
Stress group was modeled as a binary factor taking the value of 1 for participants in the Stress group and 0 for controls.
Perceived stress levels were measured using a visual analog scale and normalized (z-scored) across participants.
Cortisol response was calculated as the Area Under the Curve with respect to ground after (Pruessner et al., 2003) over the course of the whole study session (from minute +1 to minute +70) and normalized (z-scored) across participants.

Table S2. Probability of self-control failure by stress treatment group, perceived stress level and *rank transformed cortisol** response (Related to Figure 3A).

Regressor	*Estimate*	*Std. Error*	*z value*	*p(z)*
Intercept	-0.15	0.35	-0.43	0.67
Stress group (S)	0.22	0.44	0.50	0.62
Ranked Cortisol (RCORT)	-0.12	0.38	-0.33	0.74
Perceived Stress Level (PSL)	-0.12	0.34	-0.35	0.73
H_{diff}	**-1.01**	**0.09**	**-11.05**	**< 2e-16**
T_{diff}	**0.43**	**0.07**	**5.79**	**7e-09**
Recommendation (Rec)	**-0.55**	**0.07**	**-7.41**	**1e-13**
S X RCORT	0.28	0.45	0.62	0.54
S X PSL	0.02	0.43	0.05	0.96
RCORT X PSL	0.00	0.40	0.00	1.00
S X H_{diff}	0.05	0.12	0.44	0.66
RCORT X H_{diff}	0.10	0.09	1.05	0.29
PSL X H_{diff}	**0.25**	**0.09**	**2.84**	**0.005**
S X T_{diff}	**0.41**	**0.10**	**4.07**	**0.00005**
RCORT X T_{diff}	0.03	0.09	0.33	0.74
PSL X T_{diff}	0.01	0.07	0.19	0.85
S X Rec	-0.13	0.09	-1.36	0.17
RCORT X Rec	0.19	0.08	2.40	0.02
PSL X Rec	0.17	0.07	2.33	0.02
S X RCORT X PSL	-0.08	0.46	-0.17	0.86
S X RCORT X H_{diff}	-0.20	0.11	-1.78	0.07
S X PSL X H_{diff}	-0.16	0.11	-1.48	0.14
RCORT X PSL X H_{diff}	0.08	0.09	0.91	0.36
S X RCORT X T_{diff}	-0.16	0.11	-1.50	0.13
S X PSL X T_{diff}	**0.24**	**0.10**	**2.40**	**0.02**
RCORT X PSL X T_{diff}	0.15	0.09	1.69	0.09
S X RCORT X Rec	**-0.22**	**0.09**	**-2.38**	**0.02**
S X PSL X Rec	-0.16	0.09	-1.78	0.08
RCORT X PSL X Rec.	0.05	0.08	0.58	0.56
S X RCORT X PSL X H_{diff}	-0.09	0.11	-0.82	0.41
S X RCORT X PSL X T_{diff}	-0.15	0.11	-1.31	0.19
S X RCORT X PSL X Rec.	-0.14	0.10	-1.50	0.13

*This additional replication of the regression in Table S1 above was run to test whether the distribution of the non-linear cortisol AUC measure had a strong impact on the regression coefficients. The results indicate that this was not the case.
Cortisol response was calculated as the Area Under the Curve with respect to ground after (Pruessner et al., 2003) over the course of the whole study session (from minute +1 to minute +70) and then rank transformed across participants.
All other details are identical to Table S1.

Table S3. Probability of self-control failure by stress treatment group, perceived stress level and cortisol response *controlling for hunger level* (Related to Figure 3A).

Regressor	*Estimate*	*Std. Error*	*z value*	*p(z)*
Intercept	-0.07	0.37	-0.19	0.85
Stress group (S)	0.11	0.47	0.24	0.81
Cortisol (CORT)	-0.07	0.36	-0.20	0.84
Perceived Stress Level (PSL)	-0.23	0.37	-0.62	0.54
H_{diff}	**-1.01**	**0.09**	**-11.08**	**< 2e-16**
T_{diff}	**0.43**	**0.07**	**5.74**	**9e-09**
Recommendation (Rec)	**-0.54**	**0.07**	**-7.39**	**1e-13**
Hunger level	*-0.30*	*0.54*	*-0.55*	*0.58*
S X CORT	0.21	0.44	0.49	0.63
S X PSL	0.08	0.45	0.18	0.86
CORT X PSL	0.07	0.36	0.18	0.85
S X H_{diff}	0.06	0.12	0.52	0.60
CORT X H_{diff}	0.11	0.09	1.19	0.23
PSL X H_{diff}	**0.25**	**0.09**	**2.84**	**0.005**
S X T_{diff}	**0.42**	**0.10**	**4.23**	**0.00002**
CORT X T_{diff}	0.04	0.09	0.46	0.64
PSL X T_{diff}	0.01	0.07	0.11	0.91
S X Rec	-0.14	0.09	-1.50	0.13
CORT X Rec	**0.18**	**0.08**	**2.31**	**0.02**
PSL X Rec	**0.18**	**0.07**	**2.47**	**0.01**
S X Hunger level	*0.10*	*0.58*	*0.17*	*0.86*
S X CORT X PSL	-0.11	0.43	-0.26	0.80
S X CORT X H_{diff}	-0.20	0.11	-1.85	0.07
S X PSL X H_{diff}	-0.17	0.11	-1.55	0.12
CORT X PSL X H_{diff}	0.08	0.08	0.96	0.34
S X CORT X T_{diff}	-0.14	0.10	-1.36	0.17
S X PSL X T_{diff}	**0.24**	**0.10**	**2.41**	**0.02**
CORT X PSL X T_{diff}	**0.18**	**0.08**	**2.20**	**0.03**
S X CORT X Rec	**-0.22**	**0.09**	**-2.33**	**0.02**
S X PSL X Rec	-0.17	0.09	-1.81	0.07
CORT X PSL X Rec	0.02	0.07	0.27	0.79
S X CORT X PSL X H_{diff}	-0.07	0.10	-0.68	0.50
S X CORT X PSL X T_{diff}	**-0.20**	**0.10**	**-1.93**	**0.05**
S X CORT X PSL X Rec	-0.10	0.09	-1.12	0.26

This additional replication of the regression in Table S1 above was run to test whether hunger level had an impact on self-control choices. The results indicate that this was not the case.
Hunger levels were measured using a visual analog scale and normalized (z-scored) across participants. All other details are identical to Table S1.

Table S4. The influence of stress on choice reaction times (Related to Figure 3).

Regressor	*Estimate*	*Std. Error*	*t value*	*p(z)*
Intercept	0.425	0.044	9.765	1e-12
Stress group (S)	-0.021	0.056	-0.374	0.710
Perceived Stress Level (PSL)	0.014	0.044	0.324	0.748
Cortisol (CORT)	-0.029	0.047	-0.622	0.537
T_{diff}	-0.011	0.006	-1.889	0.059
H_{diff}	**-0.100**	**0.006**	**-17.104**	**< 2e-16**
Recommendation (Rec)	**-0.032**	**0.005**	**-5.858**	**5e-09**
MHLT	**0.033**	**0.011**	**3.031**	**0.002**
LHMT	**0.059**	**0.014**	**4.202**	**0.00003**
S X PSL	-0.026	0.055	-0.480	0.634
S X CORT	0.047	0.057	0.830	0.411
PSL X CORT	-0.008	0.047	-0.166	0.869
S X T_{diff}	**-0.018**	**0.007**	**-2.438**	**0.015**
PSL X T_{dff}	-0.002	0.006	-0.441	0.659
CORT X T_{diff}	**-0.012**	**0.006**	**-1.951**	**0.051**
S X H_{diff}	**0.018**	**0.008**	**2.452**	**0.014**
PSL X H_{diff}	**0.012**	**0.006**	**1.977**	**0.048**
CORT X H_{diff}	0.000	0.006	-0.014	0.989
S X Rec	0.002	0.007	0.242	0.808
PSL X Rec	0.005	0.006	0.838	0.402
CORT X Rec	0.001	0.006	0.132	0.895
S X MHLT	**0.033**	**0.015**	**2.302**	**0.021**
PSL X MHLT	-0.014	0.011	-1.248	0.212
CORT X MHLT	-0.019	0.014	-1.371	0.171
S X LHMT	0.006	0.017	0.339	0.735
PSL X LHMT	-0.012	0.014	-0.839	0.402
CORT X LHMT	-0.014	0.013	-1.076	0.282
S X PSL X CORT	-0.061	0.055	-1.113	0.272
S X PSL X T_{diff}	**-0.020**	**0.007**	**-2.750**	**0.006**
S X CORT X T_{diff}	0.014	0.008	1.824	0.068
PSL X CORT X T_{diff}	-0.022	0.006	-3.551	0.0004
S X PSL X H_{diff}	0.006	0.007	0.856	0.392
S X CORT X H_{diff}	-0.008	0.008	-1.035	0.301
PSL X CORT X H_{diff}	0.005	0.006	0.843	0.399
S X PSL X Rec	-0.002	0.007	-0.336	0.737
S X CORT X Rec	-0.004	0.007	-0.500	0.617
PSL X CORT X Rec	0.009	0.006	1.456	0.145
S X PSL X MHLT	**0.047**	**0.015**	**3.123**	**0.002**
S X CORT X MHLT	0.010	0.016	0.622	0.534

PSL X CORT X MHLT	-0.024	0.015	-1.644	0.100
S X PSL X LHMT	0.032	0.017	1.919	0.055
S X CORT X LHMT	0.018	0.017	1.085	0.278
PSL X CORT X LHMT	-0.021	0.013	-1.579	0.114
S X PSL X CORT X T_{diff}	**0.033**	**0.007**	**4.538**	**0.000006**
S X PSL X CORT X H_{diff}	0.002	0.007	0.208	0.836
S X PSL X CORT X Rec	-0.007	0.007	-0.980	0.327
S X PSL X CORT X MHLT	0.013	0.017	0.795	0.427
S X PSL X CORT X LHMT	0.022	0.016	1.383	0.167

Estimates are regression coefficients from a mixed-effects generalized linear model fit by restricted maximum likelihood. P-values for t-tests on regression coefficients use the Satterthwaite approximation to degrees of freedom.
H_{diff} is the absolute health difference between both items; T_{diff} is analogously the absolute taste difference between both items.
Recommendation was modeled with the value of 1 for a healthy recommendation, 0 for no recommendation, and -1 for an unhealthy recommendation.
Choose Healthier & Less Tasty (MHLT; self control success) and choose Tastier & Less Healthy (LHMT; self-control failure) were modeled as a binary factor taking the value of 1 whenever such a choice occurred, and 0 otherwise.
Stress group was modeled as a binary factor taking the value of 1 for participants in the Stress group and 0 for controls.
Perceived stress levels were measured using a visual analog scale and normalized (z-scored) across participants.
Cortisol response was calculated as the Area Under the Curve with respect to ground after (Pruessner et al., 2003) over the course of the whole study session (from minute +1 to minute +70) and normalized (z-scored) across participants.

Table S5. This table represents the results of an additional control analysis examining the probability of choosing the left item in trials with no self-control challenge (i.e. tastier food = healthier food). (Related to Figure 2C).

Regressor	*Estimate*	*Std. Error*	*z value*	*p(z)*
Intercept	0.14	0.17	0.83	0.41
Stress group (S)	-0.14	0.22	-0.61	0.54
Taste left item	**0.61**	**0.08**	**7.25**	**4e-13**
Taste right item	**-0.56**	**0.08**	**-6.65**	**3e-11**
Health left item	**1.26**	**0.10**	**12.98**	**< 2e-16**
Health right item	**-1.28**	**0.10**	**-13.37**	**< 2e-16**
Recommendation left item	**0.64**	**0.20**	**3.25**	**0.001**
Recommendation right item	**-0.67**	**0.20**	**-3.41**	**0.0006**
Stress X Taste left	**0.29**	**0.12**	**2.45**	**0.01**
Stress X Taste right	-0.21	0.12	-1.85	0.06
Stress X Health left	**-0.29**	**0.13**	**-2.26**	**0.02**
Stress X Health right	0.23	0.13	1.80	0.07
Stress X Recommend left	-0.11	0.26	-0.43	0.66
Stress X Recommend right	-0.07	0.26	-0.27	0.79

Because the healthier food is also the tastier food in these cases, there is no need to inhibit button press responses indicating a choice for the tastier food in these trials. The significant Stress X Taste and Stress X Health interactions in this regression and the reaction time results summarized in Table S2 indicate that the stress induction procedure changes the impact of taste and health attributes on choice in a manner that goes beyond simply impairing response inhibition mechanisms.

Estimates are logistic regression coefficients from a mixed-effects generalized linear model fit by maximum likelihood.

Taste and health coefficients denote the normalized (z-scored) taste and health rating for the item presented on the screen (left and right).

Recommendation left was modeled as a binary factor taking the value of 1 when the item on the left side of the screen was recommended 0 otherwise. Recommendation right is the analogous binary regressor for trials in which the item on the right side of the screen was recommended.

Stress group was modeled as a binary factor taking the value of 1 for participants in the Stress treatment group and 0 for the Control treatment group.

Table S6. Regions showing a positive correlation with the subjective value of the chosen food item and the difference between chosen and non-chosen items across participants in both groups (Related to the 3D rendering in Figure 5).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Chosen food value			
Cuneus	R	3 -85 15	8.09
Posterior Middle Temporal Gyrus	L	-60 -40 -10	6.97
Inferior Lateral Occipital Cortex	R	55 -70 -7	6.36
vmPFC: Medial Orbitofrontal cortex	L	-5 61 -0	6.2
Planum Temporale	L	-62 -20 9	6.15
Angular Gyrus	R	53 -57 15	6.09
Occipital Pole	L	-10 -95 28	6.03
Inferior Temporal Gyrus	R	73 -32 -19	5.97
Precuneus	L	-5 -82 43	5.84
Lingual Gyrus	R	16 -52 -4	5.83
Middle Temporal Gyrus	R	68 -47 -4	5.67
Frontal Medial Cortex	R	1 46 -19	5.67
Amygdala	L	-27 -5 -10	5.61
Lateral Occipital cortex	L	-52 -67 15	5.5
Precentral Gyrus	L	-15 -27 77	5.42
Brain Stem	L	-15 -25 -28	5.38
Frontal Pole	L	-17 56 37	5.35
vmPFC: Rostral Anterior Cingulate Gyrus	L	-10 38 3	5.3
Middle Temporal Gyrus	R	63 -2 -22	5.22
Precuneus	R	1 -70 59	5.2
Postcentral Gyrus	R	23 -27 59	4.84
Frontal Orbital Cortex	L	-20 18 -25	3.23
Left Hippocampus	L	-20 -15 -19	3.48
Inferior Frontal Gyrus, Pars Triangularis	L	-55 26 12	3.5
Middle Frontal Gyrus	L	-42 -2 65	4.24
Inferior Frontal Gyrus, Pars Opercularis	R	63 26 3	3.9
Chosen minus Nonchosen food value			
Posterior Middle Temporal Gyrus	L	-60 -40 -7	6.51
Central Opercular Cortex	L	-62 -22 15	6.45
Posterior Superior Temporal Gyrus	R	66 -25 21	6.42
Putamen	L	-30 -17 3	6.35
Temporooccipital Middle Temporal Gyrus	R	63 -52 -4	6.35
Temporooccipital Middle Temporal Gyrus	L	-50 -62 9	6.27
Temporooccipital Inferior Temporal Gyrus	R	41 -45 -7	6.22
Occipital Fusiform Gyrus	R	31 -65 -22	5.87
Middle Temporal Gyrus	R	71 -20 -10	5.73

Planum Polare	R	56 -2 3	5.67
Putamen	R	28 -2 3	5.64
Amygdala	L	-22 -2 -10	5.56
Temporal Occipital Fusiform Cortex	L	-47 -62 -25	5.56
Brain Stem	R	13 -35 -19	5.53
Anterior Middle Temporal Gyrus	L	-57 3 -19	5.51
Precentral Gyrus	L	-60 -2 6	5.49
Precentral Gyrus	R	21 -25 59	5.43
Postcentral Gyrus	L	-17 -37 80	5.42
Cuneus	R	1 -85 28	5.42
Middle Temporal Gyrus	L	-70 -17 -7	5.29
Angular Gyrus	R	53 -45 59	2.69
Lateral Occipital Cortex	R	46 -82 -22	2.94
Frontal Pole	L	-20 58 37	3.81
Occipital Pole	R	18 -95 12	2.6
Temporal Pole	L	-17 16 -38	2.42
Precentral Gyrus	L	-7 -17 68	2.56
Postcentral Gyrus	L	-40 -17 37	2.19

All reported regions were significant at $p < .05$ after whole brain family-wise error correction. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Automated Anatomical Labeling (AAL (Tzourio-Mazoyer et al., 2002)) and Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Table S7. Regions showing stronger correlations with relative taste value in the Stress versus Control group (Related to Figure 3B).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Hippocampus / Amygdala	L	-27 -10 -22	4.95
Amygdala	R	13 -10 -13	4.25
Nucleus accumbens	R	6 11 -7	4.41
Amygdala	R	26 1 -19	3.77

Results represent the peak coordinates for the contrast of Tc minus Tnc from GLM-HT. The reported regions were significant at $p < .05$ after family-wise error correction in a region of interest composed of bilateral Nucleus accumbens and Amygdala. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Table S8. Regions showing stronger coupling with vmPFC during tastier choices in Stress compared to Control participants (Related to Figure 4).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Central Opercular Cortex	L	-45 -5 6	4.57
Heschl's Gyrus / Insular Cortex	L	-35 -25 15	3.23
Temporal Pole	L	-30 6 -38	3.93
Anterior Parahippocampal Gyrus	L	-22 -12 -28	3.75
Precentral Gyrus	R	46 -10 49	4.67
Planum Temporale	R	61 -22 9	4.07
Central Opercular Cortex / Insular Cortex	R	38 -15 18	4.81
Posterior Temporal Fusiform Cortex	L	-40 -15 -28	4
Superior Temporal Gyrus	L	-62 -2 0	3.82
Central Opercular Cortex	R	43 3 12	4.05
Frontal Orbital Cortex	L	-22 8 -10	4.44
White Matter (near Precentral Gyrus)	L	-27 -22 34	5.1
Temporal Pole	R	58 8 -7	4.49
Planum Temporale / Superior Temporal Gyrus	L	-65 -20 9	3.89
Central Opercular Cortex / Heschl's Gyrus	R	53 -12 9	4.14
Putamen / Nucleus accumbens*	L	-15 13 -13	4.05
Superior Temporal Gyrus	L	-52 -10 -10	4.96
Temporal Pole	L	-42 18 -25	4.61
Inferior Frontal Gyrus, pars opercularis	L	-40 -15 18	3.51
Amygdala*	L	-22 -2 -22	3.82
Hippocampus	L	-30 -10 -22	3.55

Results represent the peak coordinates for the tastier choice PPI. All reported regions were significant at $p < .05$ after whole brain family-wise error correction. The regions of amygdala and putamen/nucleus accumbens marked with asterisks are also the peaks for a small volume correction conducted within a region of interest composed of bilateral Nucleus accumbens and Amygdala. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Table S9. Regions in which vmPFC PPI during tastier food choices is more strongly correlated with cortisol than perceived stress level (Related to Figure 5).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Putamen	L	-22 -2 6	4.64
Inferior Frontal Gyrus pars triangularis	L	-47 31 6	4.46
Middle Frontal Gyrus	L	-37 8 37	4.31
Middle Frontal Gyrus	L	-42 31 28	4.26
Postcentral Gyrus	L	-62 -15 28	4.12
Thalamus	L	-25 -22 15	4.11
Postcentral Gyrus	L	-30 -35 49	4.04
Inferior Frontal Gyrus p. operc./ Precentral Gyrus	L	-52 8 18	3.79
Superior Lateral Occipital Cortex	L	-32 -60 40	3.62
Frontal Pole	L	-42 51 18	3.49
Frontal Pole	L	-27 46 31	3.42
Postcentral Gyrus / Superior Parietal Lobule	L	-47 -40 59	3.35
Precentral Gyrus / Postcentral Gyrus	L	-37 -12 37	3.31
Insular Cortex	L	-37 16 -4	3.3
Insular Cortex	L	-42 -5 6	3.28
Anterior Superior Temporal Gyrus	L	-60 -2 -7	3.26
Superior Lateral Occipital Cortex	L	-17 -67 55	3.03
Intracalcarine Cortex / Lingual Gyrus	R	8 -85 0	4.77
Lingual Gyrus	L	-17 -55 0	4.53
Temporooccipital Inferor Temporal Gyrus	R	48 -55 -7	4.5
Lingual Gyrus / Occipital Fusiform Gyrus	L	-17 -72 -13	4.48
Brain Stem	L	-5 -32 -7	4.19
Cerebellum (Culmen)	R	31 -45 -31	4.17
Intracalcarine Cortex / Superior Lateral Occipital Cortex	L	-17 -85 12	4.1
Lingual Gyrus	R	16 -60 -16	4.06
Superior Lateral Occipital Cortex	L	-32 -80 24	3.99
Temporal Occipital Fusiform Cortex	L	-40 -47 -28	3.61
Brain Stem	R	13 -32 -22	3.15
Occipital Pole	L	-17 -92 31	3.01
Temporooccip. Inf. Temp. Gyrus / Middle Temporal Gyrus	L	-52 -60 -7	2.99
Intracalcarine Cortex / Lingual Gyrus	R	31 -60 3	2.67
Occipital Pole	R	18 -97 12	2.59
Occipital Pole	L	-7 -95 -10	2.54
Occipital Fusiform Gyrus	R	33 -70 -22	2.38
Cerebellum (Culmen)	L	-10 -50 -19	2.31
Posterior Superior Temporal Gyrus / Supramarginal Gyrus	R	51 -35 9	4.51
Superior Frontal Gyrus	L	-15 -2 71	4.1

Precuneous Cortex	R	1 -57 56	4.46
Postcentral Gyrus	R	63 -7 24	4.06
Postcentral Gyrus	R	28 -32 71	4.24
Superior Parietal Lobule / Angular Gyrus	R	33 -50 46	3.92
Precentral Gyrus	R	13 -27 62	3.73
Postcentral Gyrus	L	-20 -40 59	3.43
Temporooccipital Inferor Temporal Gyrus	L	-50 -47 -10	4
Superior Lateral Occipital Cortex	R	28 -62 31	4.53
Middle Frontal Gyrus	R	31 8 43	4.91
Precentral Gyrus	L	-2 -17 59	3.33
Posterior Supramarginal Gyrus	R	33 -37 40	3.35
Right Caudate	R	18 21 6	3.95
Superior Lateral Occipital Cortex	R	26 -60 49	3.41
Superior Frontal Gyrus	L	-2 31 46	3.44
Postcentral Gyrus	R	36 -32 62	3.08
Postcentral Gyrus / Precuneous Cortex	R	13 -40 55	3.52
Posterior Cingulate Gyrus	L	-2 -17 46	3.33
Cerebellum (Culmen / Vermis)	L	-2 -60 -13	3.87
Precuneous Cortex	L	-5 -45 46	3.83
Inferior Lateral Occipital Cortex	R	31 -80 6	3.94
Occipital Pole	L	-5 -97 3	3.73
Superior Parietal Lobule	L	-17 -57 59	3.86
Anterior Cingulate Gyrus	L	-5 16 31	3.28
Precuneous Cortex / Postcentral Gyrus	R	16 -35 46	3.41
Anterior Cingulate Gyrus	L	-5 18 37	3.83
Temporooccipital Middle Temporal Gyrus	R	53 -50 0	2.33

Results represent the peak coordinates for the tastier choice PPI. All reported regions were significant at $p < .05$ after whole brain family-wise error correction. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Table S10. Regions showing greater activity for self-control choices (Related to the 3D rendering in Figure 5).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Middle/Inferior Frontal Gyrus	L	-45 16 31	5.3
Frontal Pole/Superior Frontal Gyrus	L	-20 56 34	5.86
Superior Parietal Lobule	L	-27 -67 55	5.61
Paracingulate/Anterior Cingulate Gyrus	L	-2 33 31	4.25
Paracingulate/Superior Frontal Gyrus	R	1 36 40	3.96
Frontal Pole/Superior Frontal Gyrus	L	-20 53 21	3.87

All reported regions were significant at $p < .05$ after whole brain family-wise error correction. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

This table is included for the facilitation of future experiments and meta-analyses. It reports uncorrected p-values that are not used as the basis for any inferences made in the current work.

Table S11. Regions showing greater activity for the contrast Unhealthy minus Healthy recommendation trials in the Stress versus Control participants (not related to any main text or figures).

Region	*Side*	*MNI Coordinates*	*T-stat*
Superior Frontal Gyrus	R	6 23 59	4.56
Inferior Frontal Gyrus, pars opercularis	L	-57 16 6	3.66
Superior Frontal Gyrus	L	-5 16 62	3.72
Frontal Pole	L	-27 41 37	3.81
Frontal Pole	L	-37 56 18	3.43
Superior Frontal Gyrus	R	23 11 49	3.66
Middle Frontal Gyrus	R	48 6 46	3.8
Paracingulate Gyrus	R	11 11 46	3.71
Precuneous Cortex	L	-25 -52 24	3.47
Frontal Orbital Cortex	L	-25 16 -19	3.41
Temporal Pole	L	-50 11 -19	3.24

All reported regions were significant at the p < .001 uncorrected level and contain at least 3 voxels. T statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Table S12. Regions in which the difference in vmPFC PPI for healthier versus tastier food choices is more strongly correlated with perceived stress level than cortisol (Related to Figure 5).

Region	*Side*	*MNI Coordinates*	*TFCE t-stat*
Occipital Fusiform Gyrus	L	-22 -75 -10	4.51
Intracalcarine Cortex	L	-7 -82 3	4.12
Occipital Fusiform Gyrus / Lingual Gyrus	R	13 -82 -13	4.15
Inferior Frontal Gyrus	L	-37 8 24	4.36
Insular Cortex	L	-30 11 6	4.72
Middle Frontal Gyrus	L	-45 31 31	3.96
Frontal Pole	L	-32 41 24	4.34
Lingual Gyrus	R	6 -72 -4	3.51

All reported regions were significant at $p < .05$ after whole brain family-wise error correction. Threshold free cluster enhancement (TFCE) test statistics were calculated with the permutation method described by (Smith and Nichols, 2009) and implemented in FSL. Sub-peaks within clusters formed by contiguous voxels are reported when separated by a distance of 20mm with a maximum of 20 sub-peaks per cluster. Anatomical labels were derived from the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006).

Supplemental Experimental Procedures

Participants

The inclusion/exclusion criteria for participants were as follows: All participants had normal or corrected-to-normal vision, were right-handed, non-smokers and refrained from taking any medication for 3 days prior to their scanning session. Individuals taking any prescription medications were excluded from participation. Participants reported no history of somatic or psychiatric disease or drug abuse. In addition, they had no history of eating disorders or food allergies and intolerances, and did not currently follow a specific diet (e.g. vegan, vegetarian, gluten-free, etc.). The mean BMI of all participants included in the fMRI study was 22.55 (± 2.06 SD). To ensure a normal reaction of the hypothalamic-pituitary-adrenal (HPA) axis, individuals who reported any history of atopic reactions (including hay fever, dermatitis, and any other allergies) were excluded from participation. To control for HPA axis reaction, participants also did not consume alcohol or caffeine in the 18 hours before the experiment, were instructed to get sufficient sleep in the night before the experiment, and refrained from exercise in the 6 hours before they came to the laboratory. They were instructed to eat a light meal (sandwich or salad) 3 hours before their appointment, and to consume nothing but water until the experiment was over. None of our volunteers had participated in a stress experiment previously (Schommer et al., 2003).

The recruitment and inclusion criteria for this study included a general desire to eat healthy and exercise, while still enjoying the consumption of junk food items. These criteria selected for individuals who would face a self-control challenge in our task. The participants' self-reported typical eating behavior indicates that our request for the participants to "choose the healthier option whenever possible" in this study is consistent with their general efforts to maintain a healthy lifestyle (see Experimental Procedures). Furthermore, we found a significant positive correlation between self-control success in our task and the restrictive eating subscale of the Three Factor Eating Questionnaire ($r = 0.30$, $p = 0.03$). Note that restrictive eating habits did not differ between Stress (median restriction score = 5 ± 1.93 MAD) and Control treatment groups (median restriction score = 6.5 ± 2.59 MAD; $z = -0.88$, $p = 0.38$).

Data of three participants had to be excluded from a subset of analyses. The swab for the baseline cortisol measurement of one participant did not contain enough saliva for analysis and was coded as missing. This participant was excluded from all analyses that involved comparison to baseline cortisol or cortisol AUC. One participant was an outlier with regard to the peak cortisol measurement and therefore was left out of any behavioral or brain analyses that involved correlations with cortisol. Omitting this outlier from comparisons of means across the treatment groups did not change the results, however. A third participant failed to complete the VAS rating for perceived stress. This participant was excluded from all analyses that involved the perceived stress level.

We restricted our sample in this initial study to men in order to establish changes in the value computation / self-control circuits in a sample of participants with a relatively homogeneous level of gonadal hormones. Sex steroids are known to modulate measures of the neuroendocrine stress response. The salivary free-cortisol response to psychosocial stress in women varies with the stage of the ovulatory cycle (pre- or post-luteal phase) as well as the use of hormonal contraception (Kirschbaum 1999, 1992). For additional details see (Hellhammer et al., 2009). In practice, ensuring the comparability between salivary cortisol measures from women and men is often achieved by testing women who are not using hormonal contraception and are in the post-luteal phase of their cycle. However, the most thorough test of the differential effect of psychosocial stress on self-control in women would require testing the same individual in both her pre- and post-ovulation phases to account for changing levels in gonadal hormones, and given the wide use of hormonal contraceptives in the population, should also include a systematic comparison of the effects of hormonal contraception use. These will be important experiments to conduct in the future.

Choice task

The position of the healthier item and the healthier recommendation were fully randomized to avoid systematic bias toward one side of the screen. The allocation of trials into recommendation conditions was also random. Choice pairs were created according the individual participants' health and taste ratings. Our matching algorithm ensured that only foods with unequal health ratings were paired in order to make sure that we could classify our recommendations as correct (i.e. for the

healthier item) or incorrect. Trials with correct, incorrect, or no recommendation were then allocated equally across the three runs, such that each run contained 40 trials with a correct recommendation, 20 trials with an incorrect recommendation, and 10 trials without a recommendation. These trial types were presented in a completely randomized order within each run.

Cortisol analysis

Salivary cortisol was analyzed by the laboratory of Prof. Clemens Kirschbaum (TU Dresden, Germany) using a commercially available competitive luminescence immunoassay (CLIA; IBL, Hamburg, Germany). The intra- and interassay coefficients of variation for cortisol were below 8%. Salivary cortisol concentrations are reported in nanomol/liter. A Kolmogorov-Smirnov-Test revealed that cortisol values were not normally distributed within the Stress group and thus statistical comparisons using cortisol values were performed with non-parametric tests. Five participants in the Stress group took their hand out of the water bath before the undisclosed 3-minute duration of the SECPT was over. When this occurred, according to the SECPT test protocol, the participants were instructed to try putting their hand back in the water if they could, and to remain still and look into the camera until the test was over. Three of the five re-inserted their hand in the cold water bath several times. In total, the five participants endured the water bath for a mean duration of 103 seconds (SD = 43 s).

The level of salivary cortisol (calculated as Area Under the Curve with respect to ground over the total time of the session after (Pruessner et al., 2003)) did not differ between participants who removed their hand (mean = 430, SD = 287) and those who did not (mean = 550, SD = 265) (Wilcoxon rank sum test $Z = -1.16$, $p = 0.25$). However, these individuals did have higher self-reported stress levels (PSL) (Wilcoxon rank sum test $Z = 2.25$, $p = 0.02$). We believe that the most likely reason for the high PSL ratings in participants who removed their hand early was a sense of failure. The participants were explicitly told that they were being evaluated during the SECPT. Removing the hand before instructed to do so meant implicitly admitting that they could not tolerate the cold water and would be evaluated negatively by the opposite sex experimenter observing them. Excluding the 5 participants who withdrew their hand early does not change any

of the relationships between stress induction, PSL, or cortisol and behavior and therefore these participants were included in all analyses.

Psychometric inventories

After the fMRI scan, participants completed German versions of the Three Factor Eating Questionnaire (Pudel and Westenhöfer, 1989), the Spielberger State-Trait Anxiety Inventory (Lane et al., 2009), and the Behavioral Inhibition and Activation Scales (Butler et al., 2006).

Self-report ratings

A Kolmogorov-Smirnov-Test revealed that values for the perceived stress level (PSL) were not normally distributed. For this reason and for consistency with the group level fMRI analyses, statistical comparisons between Stress and Control group with regard to perceived stress level were performed with non-parametric permutation tests.

Health, taste, and appetitiveness ratings

Participants used a continuous rating scale, on which anchor points were depicted in steps of 1 (range from -5 for "very untasty / unhealthy" to +5 for "very tasty / healthy"). For clarity, we report ratings as % of maximum taste or health scale value. Median taste and health ratings in the Stress and Control groups did not differ (taste Stress = 56.10%, taste Controls = 54.22%; Z = - 0.81, p = .42; health Stress = 47.42%, health Controls = 44.84%; Z = - 0.81, p = .42). The median correlation between health and taste ratings was – 0.09 ± 0.31 MAD in the Stress group, and – 0.06 ± 0.20 MAD in the Control group. Appetitiveness ratings also did not differ between the two groups (Z = -0.23, p = 0.81).

Lastly, health (r = -0.12, p = 0.40), taste (r = 0.09, p = 0.56), and appetitiveness ratings (r = 0.13, p = 0.37) were not correlated with hunger levels. For these correlations, the Pearson correlation coefficients (r) were tested against a null distribution generated from 5000 permutations of the data to compute two-tailed p-values.

Statistical Analyses

All behavioral data were analyzed using either the Matlab (Release 2012b, version 8.0.0.783, (The MathWorks Inc., 2012)) or R (Version 2.14.2 , ("R Core Team," 2014)) statistical software packages.

General linear model for RT

We modeled reaction times in a linear mixed effects model fit by restricted maximum likelihood as a function of the binary variable Group (Stress, Control), and continuous variables of PSL and cortisol level at the subject level and the difference in health and taste between both items, the recommendation, and the type of choice a participant made with regard to taste and health (binned by higher and lower health and taste combinations) at the trial level. The model included all one, two, and three way interactions between subject level variables and the three trial level variables (see Table S2 for full the listing). For clarity we present the model with only trial level variables below.

$$RT = \beta_0 + \beta_1 HRec + \beta_2 MHLT + \beta_3 LHMT + \beta_4 T_{diff} + \beta_5 H_{diff} + \varepsilon$$

RT is the log transformed reaction time on each trial. HRec takes the value of 1 whenever the healthier food is recommended, 0 when there is no recommendation, and -1 when the less healthy food is recommended. MHLT is a binary regressor taking the value of 1 whenever a healthier, but less tasty food is chosen and 0 otherwise. LHMT is a binary regressor taking the value of 1 whenever a less healthy, but tastier food is chosen and 0 otherwise. T_{diff} is the absolute value of the difference in taste ratings between the two foods, and H_{diff} is the absolute value of the difference in health ratings between the two foods. The subject level variables PSL and cortisol were z-scored across participants.

fMRI data acquisition

Images were acquired using a Philips Achieva 3 T whole-body scanner with an eight-channel sensitivity-encoding head coil (Philips Medical Systems) at the Laboratory for Social and Neural Systems Research, University Hospital Zurich. Stimulus presentation was controlled with the

Psychophysics Toolbox Software (Psychtoolbox 3.0, (Brainard, 1997)); the paradigm was presented via a back-projection system to a mirror that was mounted on the head-coil.

We acquired gradient echo T2*-weighted echo-planar images (EPIs) with blood-oxygen-level-dependent (BOLD) contrast (41 slices per volume, Field of View 200 x 126.5 x 200 mm, slice thickness 2.5 mm, 0.6 mm gap, in-plane resolution 2.5*2.5 mm, matrix 80*80, repetition time 2460 ms, echo time 30 ms, flip angle 77°) and a SENSE reduction (i.e. acceleration) factor of 2. Volumes were acquired in axial orientation at a +15° tilt to the anterior commissure-posterior commissure line. We collected 161 volumes in ascending order during each of the three experimental runs, together with five "dummy" volumes at the start and end of each run. A T1-weighted turbo field echo structural image was acquired in sagittal orientation for each participant at the end of the scanning session with the same angulation that applied to the functional scans (181 slices, Field of View 256 x 256 x 181 mm, slice thickness 1 mm, no gap, in-plane resolution 1*1 mm, matrix 256*256, repetition time 8.4 ms, echo time 3.89 ms, flip angle 8°). To measure the homogeneity of the magnetic field we collected B0/B1 maps before the first and second run and before acquiring the structural scan (short echo time = 4.29 ms, long echo time = 7.4 ms). We measured breathing frequency and took an electrocardiogram with the in-built system of the scanner in order to correct for physiological noise.

fMRI Preprocessing

Statistical parametric mapping (SPM8, Update Rev. Nr. 5236; Functional Imaging Laboratory, University College London) was used to spatially realign and unwarp functional data, segment them according to the corresponding T1-weighted high resolution structural image and normalize them to the participant's mean EPI template. Images were smoothed using an isometric Gaussian kernel (4 mm full width at half maximum). As physiological noise may disturb the BOLD signal and account for fluctuations, we used RETROICOR, as implemented in the PhysIO toolbox, to model respiration and heartbeat (Glover et al., 2000). The implementation of RETROICOR we used, the PhysIO Toolbox (Kasper, 2009), is open source code available as part of the TAPAS software collection: www.translationalneuromodeling.org/tapas/. This algorithm uses Fourier expansions of different order for the estimated phases of cardiac pulsation (3rd order), respiration (4th order) and cardio-respiratory interactions (1st order) following (Harvey et al., 2008). For two

participants, physiological data from the scan were not saved due to a technical problem. For these participants, we applied only the standard motion correction procedure as implemented in SPM 8.

Figures for depicting the fMRI results were created with the MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) and MRIcro GL software (http://www.mccauslandcenter.sc.edu/mricrogl/; (Rorden and Brett, 2000)).

Augmented GLM-health, taste value (HT-FVdiff)

In GLM-HT-FVdiff, we augmented our GLM-HT to examine the effects of health, taste, and recommendations on BOLD activity using a model with regressors identifying five events of interest: 1) all choice onsets, 2) trials in which the healthier food was recommended and chosen, 3) trials in which the healthier food was recommended and not chosen, 4) trials in which the less healthy food was recommended and chosen, 5) trials in which the less healthy food was recommended and not chosen. In this augmented version that accounts for the discriminability of the food options, five parametric modulators were included with the first regressor for all choices: P1) Difference between the chosen and non-chosen food value (FVdiff), P2) Health rating for chosen item (Hc), P3) Taste rating for chosen item (Tc), P4) Health rating for non-chosen item (Hnc), P5) Taste rating for non-chosen item (Tnc). These parametric regressors were orthogonalized with respect to one another. All regressors were defined as boxcar functions with duration equal to the reaction time on that trial. Regressors for head motion, cardiac, and respiratory effects were included to account for BOLD signal variability associated with these effects.

Following the estimation of GLM-HT for each participant, we computed first level contrasts for: 1) Tc-Tnc, 2) FVdiff. Next, we computed a two-sample t-test between the Stress and Control groups comparing the relative taste value (Tc–Tnc) and food value difference (FVdiff) signals. In the relative taste value analysis, we corrected for multiple comparisons within the same anatomically defined ROI as in GLM-HT, encompassing all voxels with a non-zero probability of belonging to the bilateral amygdalae or nucleus accumbens as defined by the Harvard-Oxford subcortical atlas (Desikan et al., 2006).

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C. Appendix to Study 3

Higher heart rate variability is associated with increased resistance to temptation in the face of dietary self-control challenges

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Abstract

Self-control has been linked to better psychosocial and physical health. Yet it is unclear through which channels this link may operate. A similar link to health outcomes has been reported for heart rate variability (HRV). We therefore tested in a food choice self-control task whether HRV at sedentary rest can serve as a biomarker for the neurophysiological adaptability that putatively underlies self-controlled behavior, and whether individuals with higher HRV are more resilient against self-control temptations following stress. We found HRV to be as highly associated with self-control in dietary choice as an established psychometric scale of restrained eating (RSE), and that individuals with higher HRV were better able to down-regulate their cravings in the face of taste temptations. Moreover, combining HRV and RSE in our behavioral model improved the prediction of self-control levels. Furthermore, HRV was associated with activity patterns in the ventromedial prefrontal cortex, a key node in the brain's valuation and decision networks. Specifically, individuals with higher HRV showed both higher overall BOLD activity and attenuated taste representations when presented with a dietary self-control challenge as compared to choices that did not require self-control to override taste preferences. Lastly, the behavioral and neural associations with HRV remained consistent when participants were subjected to an acute laboratory stressor before making their decisions. The stability of this association suggests that HRV may serve as a robust biomarker for self-control ability across environmental contexts.

Introduction

Self-regulation is a central ability that has been associated with a wide range of positive life outcomes, from higher socio-economic status to better mental and physical health (Mischel et al., 1989; Duckworth, 2011; Moffitt et al., 2011). To date it is not clear, however, through which channel self-regulation and health are linked. Does being in good health make self-regulation easier? Or are good regulators healthier, because they react sooner or more appropriately to potential problems and thus maintain their health more effectively? Initial evidence suggests that trait characteristics such as conscientiousness and emotional stability are associated with better health outcomes (Smith, 2006; Martin et al., 2007; Deary et al., 2008; Terracciano et al., 2008). These same characteristics may also be integral to practicing self-control. Whether these traits directly influence health by changing health behavior (e.g., by using self-control to monitor and correct deviations), or indirectly by moderating the way we react to stressors and challenges in daily life (i.e., by initiating coping strategies earlier) and to which stressors we respond at all, or whether they form a predisposition that expresses itself both in health outcomes and personality traits still remains to be investigated (Smith, 2006).

Self-regulation is often assessed by psychometric questionnaires or behavioral paradigms. More comprehensive measures such as "360 degree interviews" can also be employed. For example, Moffitt et al. (2011) not only assessed children, but also asked parents and teachers to rate the children's' abilities in various self-control related domains in order to create a combined measure of self-control that was used to predict life outcomes. However, the collection of these more comprehensive measures is often impractical. Unfortunately, the more feasible questionnaire- and experiment-based methods can be distorted by strategic answering, for example if participants try to show themselves in a better light by reporting socially desirable answers or try to behave according to the presumed goals of the experimenter (experimenter-demand effects) during behavioral studies. Therefore, measures that are easy to obtain, but less prone to biases in reporting strategies or task performance, such as physiological readouts, would be an important addition to the investigator's toolkit in order to improve the prediction of later self-control performance.

Links between self-regulation and heart rate variability have been described in the literature for a couple of decades now, raising the question whether HRV might be a suitable predictor of self-regulation capacities of an individual. Heart rate variability is an essential characteristic of the heart in vertebrates (Grossman and Taylor, 2007): the time between subsequent beats oscillates on the order of milliseconds and no two beat pairs (RR intervals) directly following each other are of exactly the same length (Camm et al., 1996). While HRV can be reduced temporarily during physically or mentally straining tasks (Porges and Raskin, 1969), differences in resting HRV appear to distinguish between states of health and disease. High resting HRV has been associated with both physical (Masi et al., 2007) and mental health (Thayer and Brosschot, 2005), and chronic decreases in HRV mark a state of disease. Individuals with a low heart rate variability were shown to recover slower from psychological stressors, as assessed by cardiovascular, endocrine, and immune responses (Weber et al., 2010). In addition, individuals with a high Cortisol Awakening Response (CAR) that is indicative of high chronic stress were shown to have a low HRV (Stalder et al., 2011). Earlier work in the domain of emotion regulation suggests that heart rate variability (HRV) may index both self-regulatory capacities (in baseline / resting HRV measurements) and performance (in HRV measured during regulation tasks), but further links to other domains of self-regulation remain to be tested. Overall it seems that HRV might serve as readout of an individual's allostatic capacities that help to integrate behavioral strategies and energy household in response to demands in the environment, and higher HRV would putatively mark better capacities for allostatic regulation (Grossman and Taylor, 2007).

HRV can be calculated in two different domains: time and frequency. The full range of measures is discussed in the guidelines by the Task Force on HRV (Camm et al., 1996). Time domain measures have the advantage of being more robust than frequency measures. Two different time domain measures are commonly used and both characterize the distribution of inter-beat intervals, which are defined as the time between two subsequent heart beats (i.e., the difference between two R peaks in the ECG (Guyton and Hall, 2006), hence also called "RR interval"). The standard deviation of all RR (also "NN" for "normal-to-normal") intervals, SDNN, describes the total heart rate variability within a given

period (see equation 1 in the Methods). The root mean square of successive differences (RMSSD) calculated between adjacent RR intervals is more sensitive to influences of short-term regulation of the heartbeat (see equation 3 in the Supplemental Methods). Here we focus on HRV at rest (i.e. in the absence of specific, discrete input stimuli), and thus take SDNN as our primary measure of variability.

Thus far, heart rate variability and self-regulation have been investigated primarily in the domain of emotional responses and regulation (for a review see Kreibig (2010)). One of the most prominently discussed regulation processes is the re-allocation of attention (e.g., disengaging attention from stimuli that are not threatening) that may promote a reduction of allostatic load (McEwen and Wingfield, 2003) by disengaging attention and relaxing once a challenge is over. Healthy individuals with a high HRV show: 1) a more pronounced decrease in startle response following safety signals (Ruiz-Padial et al., 2003; Melzig et al., 2009), 2) stronger and more rapid extinction of conditioned fear reactions (Pappens et al., 2014), and 3) smaller negativity bias and greater willingness to approach novel objects (Shook et al., 2007). Conversely, individuals with a low HRV show increased startle responses to neutral pictures compared to positive pictures and their startle response does not differentiate between neutral and negative stimuli (Ruiz-Padial and Thayer, 2014), pointing to a maladaptive negativity bias that may increase allostatic load.

Higher HRV has also been associated with better emotion regulation. During tasks that involve active regulation of emotions, HRV has been shown to increase in successful regulators during active regulation compared to situations that require low self-regulatory effort (Ingjaldsson et al., 2003; Appelhans and Luecken, 2006; Butler et al., 2006; Segerstrom and Nes, 2007; Geisler and Kubiak, 2009; Smith et al., 2011). Moreover, individuals with better emotion regulation show higher resting HRV (Appelhans and Luecken, 2006).

In the domain of self-control, low HRV has been associated with behavioral disinhibition and dysregulated social conduct (for a review see Beauchaine (2001)). A recent study by Daly and colleagues found that high trait self-control (self-reported by 198 participants on the Self-Control Scale by Tangney, Baumeister & Boone (2004)) predicted low resting heart rate and high resting

heart rate variability, and a steep decline in cortisol between measurements of the cortisol awakening response (CAR) and evening salivary cortisol (Daly et al., 2014). The study used the Day Reconstruction Method by Kahneman, Krueger, Schkade, Schwarz & Stone (2004) that helps participants recall the previous day as a sequence of episodes between 20 and 120 minutes length and report their affect during experiencing these episodes. Participants with high trait self-control reported more stable emotions, a trait that moderated the link between self-control and diurnal cortisol slope. Daly and colleagues concluded that stable affect might be one channel through which self-control relates to psychological functioning and potentially health. High trait self-control participants in their sample were also less often smokers, and smoking was found to correlate with lower HRV. However, as the authors acknowledge, their findings rely on self-reports and do not include an empirically observable measure of self-control.

Beyond these initial findings, the existence and nature of a common underlying factor relating HRV and self-control levels remains to be determined. It might be a physical factor, such as fitness, if that factor helps to improve basic cognitive functions as initial evidence suggests. It might also be some type of cognitive flexibility that helps individuals to remain calm in the face of challenges because they can more easily put experiences and perceptions into perspective, helping them to realize that they do not need to act upon a situation or that they have the means to cope with it, which would consequently also lower the allostatic load (McEwen, 1998; McEwen and Wingfield, 2003) they experience. A lower allostatic load would result in less strain on the cardiovascular system, thereby facilitating better levels of HRV.

It is also worth noting that HRV has been linked to both higher persistence and working memory. The link between HRV and persistence was shown during an unsolvable anagram task (Reynard et al., 2011) and better performance in executive function tasks, particularly those involving working memory have been reported in two separate studies (Gianaros et al., 2004; Hansen et al., 2004). There may be substantial overlap in the neural systems that support performance on persistence and working memory tasks and those that support the use of self-control because self-control often requires both working-memory (to keep your goals in mind) and persistence in the face of frustration. However, successful goal-

directed self-regulation does not rely only on the existence of sufficient working memory or persistence, but also the ability to use these capacities to achieve a goal. Interestingly, one study (Hansen et al., 2004) found improvements in executive function after a 4-week exercise program and related concurrent increases in HRV to these improvements: Exercise resulted in faster reaction times and more true positive responses in executive function tasks, whereas exercising less deteriorated physical fitness (measured as maximum oxygen consumption), resting HRV, and also resulted in a lack of learning effects (i.e. no improvement in task performance on the second test) in the executive function tasks while the training group improved on the retest. These may, however, be benefits of improved fitness that are just indexed by HRV because HRV and fitness are positively correlated. Alderman & Olson (2014) found that individuals with higher aerobic fitness (higher oxygen uptake) performed both quicker and more accurately in the congruent condition of an Eriksen Flanker Task. More fit individuals also had higher HRV, but the authors found that no additional variance was explained by HRV when controlling for fitness. However, it should be noted that performance during the congruent flanker condition does not require increased cognitive control or self-regulation in the way that the incongruent condition does. Thus, it remains to be seen whether HRV measures are equivalent to physical fitness in explaining individual differences in tasks that require self-regulation, especially in the context of a goal-directed choice.

There are two existing theories that postulate a mechanistic link between heart rate variability and self-regulation. Both the Polyvagal Theory (Porges, 1995, 2001) and the Neurovisceral Integration Theory (Thayer and Lane, 2000, 2009) try to establish a link between the central nervous system regulation of the cardiovascular system, which would be necessary to adequately prepare reactions to physical challenges or dangers in the environment, and adapt behavioral functioning at a more cognitive level. Thayer and colleagues suggest that cortical and subcortical regions involved in self-regulation share a common reciprocal inhibitory neural circuit with a network regulating the autonomic nervous system, and HRV can be used to index this network. This central autonomic network was first described by Benarroch (1993) as integrating visceromotor, neuroendocrine and behavioral responses in order to come up with adaptive behavioral answers to

current demands in the environment. It comprises ACC, insula, OFC, vmPFC, the central nucleus of the amygdala, the paraventricular nucleus of the hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, nucleus ambiguous, ventrolateral and ventromedial medulla, and the medullary tegmental field. Studies with retrograde viral labeling in rats confirmed that the prefrontal cortex is involved in vagal control of the heart (Ter Horst et al., 1996; Ter Horst, 1999). The neurovisceral integration hypothesis states that this (common) network selects and organizes responses of the organism to demands of the environment and controls physiological resources in attention and emotion (Thayer and Lane, 2009). The theory further states that the interplay between these above-mentioned regions together generates inputs to the sinoatrial node of the heart that results in the millisecond fluctuations of beat-to-beat intervals.

Porges has described these oscillations in the cardiovascular system in his Polyvagal Theory (Porges, 1995, 2001) as *vagal tone*, referring to a property of the healthy organism in which the parasympathetic branch of the autonomic nervous system is thought to control energy expenditure during resting behavior and only release its control of the heart to enable the organism to react to challenges in the environment. However, the debate on the role of parasympathetic regulation is still ongoing. Grossman & Taylor (2007) note that one observes only "final" vagal effects on the heart, but these could change because either parasympathetic regulation is withdrawn or sympathetic regulation of the heartbeat is increased, or both. Whether or not these regulatory changes are mainly due to signaling from the brain or the periphery remains unknown. Overall HRV is co-determined by other influences we have already alluded to, such as physical fitness, cardiovascular health, age, and several others (Heathers, 2014). The co-determination of HRV raises the question of the degree to which central and peripheral nervous system influences are each determining effective HRV. Berntson, Cacioppo & Grossman (2007, p. 298) suggest the more neutral term "phasic vagal cardiac control" as long as the physiological underpinnings of Polyvagal Theory cannot be clarified. Grossman and Taylor (2007) attempt to bridge Polyvagal and Neurovisceral Integration Theory. They suggest that the dynamics of high-frequency HRV reflect the organism's capacity to integrate behavioral and metabolic demands in an efficient energy exchange, and levels

outside the normal range may signal changes in a range of underlying processes, from impaired ventilatory, cardiovascular or autonomic function to psychological or behavioral disorders.

Thus, while the idea of using HRV as a biomarker for regulatory capacities is quite attractive to many researchers in cognitive neuroscience, the exact mechanisms that cause these short-term fluctuations in the system and how to pinpoint them is a matter of active debate. The methodological concerns about controlling other factors that may alter HRV (among them breathing, digestive status, etc.) necessitate cautious interpretations (see the recent review by Heathers (2014) and the special issue of Biological Psychology, 74(2), from 2007). Such concerns deserve careful consideration, and lend support to the notion that, "HRV presents an admixture of insight and significant layers of complication" (Quintana and Heathers, 2014, p. 6).

Despite its complicated nature, the association between HRV and self-regulation is a question that warrants more investigation. Although we do not fully understand the multiple cognitive and physiological factors that influence HRV, we can still assess whether this composite measure relates in a meaningful and stable way to the combination of cognitive sub-functions that together generate successful self-control. If HRV is reliably linked to self-control, then it has great promise as a quick, non-invasive, and experimenter-demand-free measure that could be used in combination with established self-report or observational measures to assess baseline self-control levels and progress after training or medical interventions.

In this study, we investigate the relationship between a behavioral measure of self-control (food choice) and resting HRV. Following the existing body of literature on self-regulation and HRV, we hypothesized that better self-control in our dietary choice task should be associated with higher heart rate variability. Specifically, we examined: (a) whether the association between HRV and self-regulation extends beyond the domain of emotions (i.e., whether HRV can be used as a potential biomarker for self-control in food choice) and (b) whether any link between HRV and self-control persists in the presence of environmental stressors. We further hypothesized that individual differences in HRV would be associated

with neural processing within a self-control network including dlPFC and vmPFC at the time of choice.

We found that higher baseline HRV was associated with better self-regulation in the dietary choice self-control paradigm. Furthermore, the pre-task, resting HRV measures were as indicative of later self-control success in the food choice task as an established psychometric index of individual restrained eating characteristics. We also found that the association between HRV and self-control holds in the face of acute stress. However, high HRV did was not associated with a reduced detrimental effect of stress on self-control (i.e. stress still impairs self-control in high HRV individuals). In addition to our behavioral links, we found that higher HRV, but not higher restrained eating, was associated with higher activity in ventromedial prefrontal cortex (vmPFC) when individuals faced challenges in self-control compared to when no challenge was present. Moreover, high HRV individuals showed a decreased sensitivity to food taste in this region of vmPFC at the time of choice. This result represents a potential neural pathway for the down-regulation of tempting taste attributes that may facilitate self-control in dietary choice.

Methods

Participants. Fifty-one men participated in this study. The sample is the same as in Maier, Makwana & Hare (2015), where we report the effects of stress on behavioral and self-control neural processes, but no heart rate analyses. Baseline HR data for two participants were lost due to recording failure. In the present report, we include the subset of participants for whom we have both heart rate and fMRI data (22 control and 27 stress group participants). The Ethics Committee of the Canton of Zurich approved this study and all participants provided written informed consent on the day of the study. Participants had been screened for eligibility in phone interviews by our recruiting team. All participants were right-handed and had normal or corrected to normal vision. None of them reported any history of somatic or psychiatric disorder, nor did they take any prescription medication. On average, participants in the sample had a blood pressure in the

(high) normal range for their age group (mean systolic blood pressure: 130 ± 14 SD; mean diastolic blood pressure: 77 ± 9).

Participants were excluded if they suffered from any allergies, food intolerances or eating disorders. We also excluded participants who followed a specific diet (e.g., eating vegetarian, vegan, gluten-free, etc.), or who did not report to enjoy and regularly consume snack foods (regularly was defined as more than two occasions per week). Eligible participants made an effort to maintain a healthy lifestyle, including exercise and an overall balanced diet. These criteria ensured that participants would face a meaningful self-control challenge in the food choice task.

To ensure a homogeneous reaction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress induction, participants were asked to abstain from drinking alcoholic or caffeinated beverages in the 18 hours before the study, to not exercise in the 6 hours prior to the study, and come to the laboratory well rested. We only recruited nonsmokers who had no history of drug abuse. We asked participants to go to bed at the latest around midnight on the day before the study and get a good night's sleep. As per standard procedure for fMRI studies in our laboratory, we instructed participants to not take any medication that alters the blood flow (e.g., analgesics) in the 72 hours before their appointment. In order to motivate food choice, participants were instructed to eat a small meal (sandwich or salad with approximately 450 kcal) 3 hours prior to the study and consume nothing but water after that.

Allen, Chambers & Towers (2007) identified age, exercise habits and obesity among others as potential confounding factors for heart rate analyses. Our sample was relatively homogeneous with regard to these factors. The men were 21.2 ± 2 years old, had a normal BMI (Mean: 22.7 ± 2.1 SD), trained on average 1.6 ± 1.4 SD times per week for building strength and had completed an average of 1.9 ± 1.3 SD cardio training sessions per week during the past four weeks before the study, resulting in a total mean of 3.6 ± 2.1 weekly training sessions per participant. The other factors identified by the Allen and colleagues, smoking, gender, caffeine and alcohol intake and circadian rhythm were controlled for by our study exclusion criteria and design.

Procedure. In the 30-40 minutes preceding the resting HRV measurement, participants had rated 180 food items for health, taste, and appetitiveness in order to create tempting food choice pairs. In the self-control choice task that followed the heart beat interval measurement and the subsequent stress induction with the Socially Evaluated Cold Pressor Test (details in Maier et al. (2015)), participants had to choose which of two items on the screen they wanted to eat at the end of the study. They were instructed to choose the healthier item as often as they could. Participants knew that one of their choices would be realized in the end, and they would have to eat whatever they chose on the trial that was randomly drawn for being paid out.

Psychometric inventories. German versions of the Spielberger State-Trait Anxiety Inventory (Laux et al., 1981), Three Factor Eating Questionnaire (Pudel and Westenhöfer, 1989), and Behavioral Inhibition and Activation Scales (Strobel et al., 2001) were administered at the end of the study. Data for the trait anxiety scale of the State-Trait Anxiety Inventory are missing for one participant, as he failed to complete the second page of the questionnaire.

Statistical Analyses. All behavioral data were analyzed using either the Matlab (Release 2014b, version 8.4.0.150421, (The MathWorks Inc., 2014)) or R (Version 3.2.1 , ("R Core Team," 2015)) statistical software packages. The fMRI results were depicted using the MRIcron software package (http://www.mccauslandcenter.sc.edu/mricro/mricron/). All correlations reported in this paper were assessed with a nonparametric bootstrap method. Two-tailed p-values for correlations were obtained by testing the Pearson correlation coefficients (r) against a null distribution generated from 5000 permutations of the data. 95 % confidence intervals for the correlations were bootstrapped over 5000 samples with a two-tailed alpha of 0.05.

Heart rate data acquisition. We measured baseline heart rate (HR) at rest with the Polar RS 800 CX system (for a cross-validation of this method with ECG see Quintana, Heathers & Kemp (2012)). All measurements were collected between 13.30 and 17.00 in the afternoon to control for circadian rhythms (Heathers,

2014). Before the HRV baseline measurement started, participants were sent to the toilet to empty their bladder in case they felt a need, so that we could proceed as quickly as possible with the fMRI scans after HR measurements and stress induction were completed. Participants were seated in a quiet room and instructed that upon mounting the Polar watch and pressing start, they would need to sit upright and calm during the subsequent baseline-recording interval.

***Heart rate analyses*.** We chose total HRV (measured as standard deviation over all RR intervals, SDNN) as our biomarker for two reasons: First, SDNN is deemed to be the most robust measure of HRV. Among all commonly computed HRV measures it has been reported to be least compromised by different data preprocessing pipelines, especially the application of artifact correction (Salo et al., 2001). Second, the process of food choice is a complex behavioral outcome that may not only depend on a capacity for effective cognitive regulation that helps to achieve self-control goals, but may also be influenced by peripheral factors (e.g., endocrine status) that are indicative of the current state of the organism. SDNN reflects all influences on the RR interval series, while it is known to correlate highly, although not perfectly, with measures that putatively reflect phasic vagal control of cardiac variability in measures taken under sedentary resting conditions (Allen et al., 2007). For comparison purposes with previous reports in the literature, we also calculated RMSSD and frequency domain measures (see the Supplemental Methods and Results and Supplemental Figures 1a-c).

The complete recording of RR intervals for each participant was extracted using the Polar software, without any transformations of the data. Three-minute intervals of the raw data were then pre-processed with the Artiifact toolbox (Version 2.08, 64-bit, (Kaufmann et al., 2011)), which has a better artifact detection rate and shows less false detections than the commonly used Kubios HRV toolbox. The Artiifact toolbox implements the algorithm of Berntson & Stowell (1998) for identifying artifacts, which aims to exclude any potential artifacts before computing the criterion for identifying true artifacts. Based on the report of Salo and colleagues (2001), who compared editing procedures for correcting single RR artifacts, the identified artifacts were deleted from the RR sequence to obtain the cleanest estimate for SDNN. On average, we corrected 2.1 ± 3.1 SD % of the RR

intervals in our sample. Apart from two datasets that had a high number of artifacts requiring correction (12.6 % and 10.5 % RR intervals removed), all other datasets had between 0 and 6% artifacts corrected (21 datasets were diagnosed as being completely artifact free). As a high number of corrected artifacts might be a concern for interpreting our findings, we check all models for robustness with regard to the number of corrected artifacts.

SDNN was calculated as

(1)

$$SDNN = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\left(RR_j - \overline{RR}\right)^2}$$

Time-domain measures of HRV were calculated with the Artiifact software suite, using Fast Fourier Transforms (Berntson and Stowell, 1998; Kaufmann et al., 2011) with an interpolation rate of 4 Hz (spline interpolation) and a Hanning window width that matched the total length of the edited recording (max. 180 seconds or slightly less in case of deletion correction). Frequency bands were bounded between 0.003 and 0.04 Hz for the very low frequency band, 0.04 and 0.15 Hz for the low frequency band, and 0.15 and 0.4 Hz for the high frequency band.

fMRI data acquisition. Images were acquired using a Philips Achieva 3 T whole-body scanner with an eight-channel sensitivity-encoding head coil (Philips Medical Systems) at the Laboratory for Social and Neural Systems Research, University Hospital Zurich. Stimulus presentation was controlled with the Psychophysics Toolbox Software (Psychtoolbox 3.0, Brainard (1997)); the paradigm was presented via a back-projection system to a mirror that was mounted on the head-coil.

We acquired gradient echo T2*-weighted echo-planar images (EPIs) with blood-oxygen-level-dependent (BOLD) contrast (41 slices per volume, Field of View 200 x 126.5 x 200 mm, slice thickness 2.5 mm, 0.6 mm gap, in-plane resolution 2.5*2.5 mm, matrix 80*80, repetition time 2460 ms, echo time 30 ms,

flip angle 77°) and a SENSE reduction (i.e. acceleration) factor of 2. Volumes were acquired in axial orientation at a +15° tilt to the anterior commissure-posterior commissure line. We collected 161 volumes in ascending order during each of the three experimental runs, together with five "dummy" volumes at the start and end of each run. A T1-weighted turbo field echo structural image was acquired in sagittal orientation for each participant at the end of the scanning session with the same angulation that applied to the functional scans (181 slices, Field of View 256 x 256 x 181 mm, slice thickness 1 mm, no gap, in-plane resolution 1*1 mm, matrix 256*256, repetition time 8.4 ms, echo time 3.89 ms, flip angle 8°). To measure the homogeneity of the magnetic field we collected B0/B1 maps before the first and second run and before acquiring the structural scan (short echo time = 4.29 ms, long echo time = 7.4 ms). We measured breathing frequency and took an electrocardiogram with the in-built system of the scanner in order to correct for physiological noise.

fMRI Preprocessing. Functional data were spatially realigned and unwarped with statistical parametric mapping software (SPM8, Update Rev. Nr. 5236; Functional Imaging Laboratory, University College London), segmented according to the participant's T1-weighted high resolution structural image and normalized to the individual mean EPI template before smoothing with an isometric Gaussian kernel (4 mm full width at half maximum). As a last step in preprocessing, we used RETROICOR, as implemented in the PhysIO toolbox, to model respiration and heartbeat (Glover et al., 2000) in order to account for fluctuations in the BOLD signal due to physiological noise. The PhysIO Toolbox by Kasper (2009) is distributed as open source code as part of the TAPAS software collection: www.translationalneuromodeling.org/tapas/. Following Harvey et al. (2008), its algorithm uses Fourier expansions of different order to the estimate the phases of cardiac pulsation (3rd order), respiration (4th order) and cardio-respiratory interactions (1st order). For two participants, the scanner could not save physiological data due to a technical problem. For these participants, only the standard motion correction procedure was applied.

fMRI analyses. In all fMRI analyses, regressors in the models were defined as boxcar functions with durations equal to the reaction time on the trial to be modeled. Each model also included regressors for head motion, respiratory, and cardiac effects on each trial to account for variance in the BOLD signal associated with these sources of noise.

Our primary general linear model (GLM-CH) tested for regions that correlated with HRV during self-control challenges (CH). The regression modeled as events of interest all trials that contained 1) a challenge, 2) no challenge, while controlling for 3) healthy and 4) less healthy recommendations. Self-control challenge and no challenge trials included parametric modulators for relative health and taste differences. We computed first-level contrasts for 1) Challenges, 2) No Challenge Trials, and 3) Challenge > No Challenge. At the second (group) level, we examined correlations with HRV the results using non-parametric permutation tests (n = 5000 permutations) with threshold-free cluster enhancement (TFCE) as implemented in the function "Randomise" in the fMRIB Software library (FSL 5, FMRIB, Winkler, Ridgway, Webster, Smith & Nichols (2014)).

An integrated value of the chosen food was calculated in a separate GLM (GLM-SV), in which parametric regressors for the integrated subjective value of the chosen and non-chosen food items modulated a regressor representing each trial 1) on which participants made a choice, while controlling for the impact of recommendations with separate regressors for events in which participants 2) chose based on our recommendation, and in which they 3) did not follow the recommendation. We modeled each participant's subjective value of food items on every trial by combining the weighted values for the taste and health of the food. The weights were derived from individual logistic regressions that assessed how much taste, health, and recommendations determined each participant's choice (identical to Maier et al. (2015)). We computed first-level contrasts for 1) the chosen and 2) non-chosen food value for each participant and extracted betas from the chosen food value contrast within our functional ROI of the ventromedial prefrontal cortex (vmPFC).

To examine the impact of health, taste, and recommendations on the BOLD signal, we calculated GLM-HT (as in Maier et al. (2015)). P-values on the

correlations were determined from 5000 permutations of the data. GLM-HT modeled five events: 1) all choices, 2) the healthier food was recommended and chosen, 3) the healthier food was recommended and not chosen, 4) the less healthy food was recommended and chosen, and 5) the less healthy food was recommended and not chosen. The first regressor for all choices included four parametric modulators: 1) health of the chosen item (Hc), 2) taste of the chosen item (Tc), 3) health of the non-chosen item (Hnc), and 4) taste of non-chosen item (Tnc). These parametric regressors were not orthogonalized with respect to one another. We computed first-level contrasts for 1) Tc, 2) Tnc, 3) Hc, 4) Hnc, 5) Tc-Tnc, and 6) Hc-Hnc. We then extracted the betas for contrasts 5 and 6 in our functional vmPFC ROIs.

The combined anatomical mask for the vmPFC was constructed from a conjunction of the bilateral frontal pole, frontal medial, paracingulate and subcallosal cortex areas that exceeded 20% probability of belonging to the respective structure in the Harvard-Oxford Cortical Atlas (HOA; Desikan et al. (2006)). In order to only consider the parts along the medial wall, the obtained anatomical mask was bounded by multiplication with a rectangular box around the midline (coordinates in MNI space: x = [- 21, 21], y = [-11, 70], z = [-35, 7]).

The anatomical mask of the left dlPFC was constructed from a conjunction of the left inferior frontal gyrus (pars opercularis and reticularis) and left superior frontal gyrus areas that exceeded 20% probability of belonging to these structures according to the HOA.

Because we tested two separate regions (vmPFC and dlPFC), we used a critical value of $p < 0.025$ (i.e. 0.05 / 2) for small volume correction.

Health, taste, and appetitiveness ratings. Participants rated health, taste, and how appetizing they found the depicted foods on a continuous rating scale with anchor points from -5 for “very untasty / unhealthy” to +5 for “very tasty / healthy”, or vice versa, to counterbalance order effects. Taste and health ratings were not correlated: the median correlation was -0.09 ± 0.31 MAD in the Stress group, and -0.06 ± 0.20 MAD in the Control group. Neither health ($r = -0.12$, $p = 0.40$), nor taste ($r = 0.09$, $p = 0.56$), nor appetitiveness ratings ($r = 0.13$, $p = 0.37$) were correlated with hunger levels.

Results

HRV. The mean duration of RR intervals across all participants was 929.3 ± 136.3 ms (sample median of the median duration of RR intervals: 947 ± 115 ms), resulting in a mean heart rate of 66 ± 10 beats per minute in our sample (values were derived after deletion of artifacts). Our participants expressed a median total HRV (measured as standard deviation over all RR intervals, SDNN) of 98.7 ± 30.1 ms median absolute deviation (MAD) within our 3-minute baseline measurement. Total HRV did not differ between the Stress (S) and Control (C) group (S: 98.7 ± 29.6 ms; C: 97.7 ± 30.9 ms, $p = 0.93$, $Z = 0.09$, Wilcoxon rank sum test). Regarding biological and psychological markers of the stress reaction, baseline SDNN and cortisol reaction (area under the curve with respect to ground (Pruessner et al., 2003)) were not significantly correlated ($r = -0.19$, $p = 0.18$), and neither were SDNN and perceived stress ($r = -0.10$, $p = 0.49$). Visual inspection of a scatter plot (see Supplemental Figure 1a) revealed one outlier in the SDNN measure: The value for this participant fell between two and three standard deviations from the mean. We therefore checked our results for robustness with and without this participant's data and found that all results remained significant.

One concern in the evaluation of heart rate variability is that applying artifact correction might inflate indices of HRV (Heathers, 2014; Quintana and Heathers, 2014) and as little as one edited artifact in the RR interval series may do so (Berntson and Stowell, 1998). We indeed observed significant positive correlations between the number of artifacts that we corrected per dataset and the SDNN ($r = 0.38$, $p = 0.008$), RMSSD ($r = 0.47$, $p = 0.008$), and HF absolute values ($r = 0.34$, $p = 0.03$). Thus, we included the number of corrected artifacts and mean heart rate as additional covariates in all of our regression models to test whether HRV indices would be predictive beyond the influence of the artifact correction and mean heart rate.

HRV and self-control behavior. Self-control success was defined as choosing the healthier, but less tasty of two food items in challenging trials in which health and taste conflicted, meaning that the participant had to overcome his own taste

preferences in order to comply with the health goal. We initially tested the relationship between total HRV (i.e. SDNN) and self-control success in a simple between-subjects correlation analysis. Total HRV was associated with the frequency of self-control success in the food choice task over all participants (Pearson r = 0.36, p = 0.01, CI = [0.07, 0.59]; all p values are derived from 5000 permutations of the data; excluding the outlying HRV participant: r = 0.33, p = 0.02, CI = [0.03, 0.58]).

Next, we modeled self-control failure (i.e., choosing a tastier, less healthy item) in a mixed-effects binomial regression (see equation 2 below) that allowed us to examine potential interactions between HRV and both trial (absolute health and taste differences, as well as our health recommendations), and participant-level (stress treatment, cognitive restraint in eating) factors. The model controlled for the expression of a restrained eating trait in order to assess whether HRV would be predictive of self-control beyond this psychometric index.

(2) SCF = Stress * HRV * (Hdiff + Tdiff + REC) + RSE

We report regression betas together with the standard error of the mean (SEM) in Table 1 (column (a)) and Figure 1. While self-control failures increased with higher taste differences between the options, higher HRV levels decreased the degree to which high taste differences led to self-control failure. At the same time, higher HRV was associated with an increased influence of health differences in reducing self-control failures. Stress separately interacted with taste difference, increasing self-control failures especially for high taste differences. However we did not observe significant three-way interactions between Stress, HRV and taste or health differences, indicating that the relationships between HRV and taste and health valuation persisted in both in the Stress and Control groups, but that HRV was not associated with resilience to the effects of acute stress.

As a biomarker of dietary self-control, total HRV explains roughly the same amount of individual variance in choice behavior as an established psychometric index of eating behavior, the restraint scale of the Three Factor Eating Questionnaire (RSE; Pudel & Westenhöfer (1989)), which was also positively associated with dietary self-control success (r = 0.35, p = 0.01, CI = [0.11, 0.55]

compared to r = 0.36 (r = 0.33 without the outlier) for HRV and self-control success; see Figures 2a and 2b). SDNN and RSE were not significantly correlated across participants (r = 0.14, p = 0.35, CI = [-0.28, 0.42]). When including RSE and HRV together in this linear regression model, both continued to explain independent and significant portions of the variance in self-control behavior. The results also hold when adding the hunger level that was measured before the start of the food choices as a covariate of no interest.

In order to assess the predictive qualities of RSE and HRV with regard to self-control in a more robust way, we predicted self-control levels out-of-sample using the leave-one-subject-out (LOSO) method. After taking one participant's data out of the sample, we fit a general linear model (GLM) that included regressors for the RSE and HRV values to explain the variance in self-control levels of the remaining participants. Using the beta coefficients from the training set, we then predicted the self-control level of the left-out participant. Squaring the obtained correlation coefficient for the true and predicted self-control levels (r = 0.36, p = 0.0048, CI = [0.14, 0.54]) yielded the coefficient of determination for the combined predictors of RSE and HRV, $r^2 = 0.13$. That is, by combining RSE and HRV, we were able to significantly predict 13% of the variation in self-control levels. HRV and RSE alone explained about half the amount of variance ($r^2 = 0.07$ and 0.06 respectively). Using the "split half" instead of LOSO method (using half the dataset for training and the other half for predicting out of sample) yielded the same result (r = 0.36, p = 0.0076, CI = [0.12, 0.54]).

As further robustness checks, we controlled for the influences of the HRV outlier and the effects of mean heart rate and artifact correction. We estimated the basic model (equation (2)) with and without the outlier (Table 1, columns (a) and (b)). Comparison of these results revealed that the interaction of health valuation and HRV seemed to be more pronounced when including the HRV outlier. When excluding his data, we still observed the relationships between taste and HRV as described above, but unlike taste, the interaction between health valuation and HRV did not reach the traditional statistical significance cutoff of 0.05 any longer (beta = -0.16 ± 0.09, z = -1.79, p = 0.07; see Table 1 column (b)). Still the estimate for the health effect without the outlier stayed within one SEM of the previous effect, indicating that this participant's scores are not solely responsible for the

association between HRV and health weighting in choice. We therefore kept his data in the other models.

To test the robustness of our model to potential confounds due to artifact correction or mean heart rate, we then added control regressors to our basic model that contained the number of artifacts corrected in each dataset and the average heart rate of the participant. Adding these additional controls to the model did not quantitatively change the results listed above. Moreover, neither the number of corrected artifacts nor mean heart rate explained a significant portion of the variance in the model (see Table 1 column (c)).

As participants knew that this study would potentially (assignment to the stress treatment was random) involve a stress procedure after the HRV baseline measurement, anticipatory anxiety would be a potential confound that might impact HRV. At the time when we took the baseline measurement, participants were not yet assigned to the stress or the control treatment. Therefore, potential anticipatory worries would affect the whole group equally. The best proxy variable to test this relationship between potential anticipatory anxiety and HRV might be the trait anxiety scale of the Spielberger State-Trait Anxiety Inventory that we collected at the end of the study for each participant (Median score: 34.5 ± 5.9 in a range of 20-80 obtainable points). We observed a negative correlation between SDNN and trait anxiety score (permutation $r = -0.26$, $p = 0.06$) that did not reach significance. When augmenting our GLM-HRV to include the trait anxiety score in our robustness check on predictors of SDNN, we observed a significant influence of trait anxiety that diminished HRV (beta = -1.62 ± 0.7, p= 0.03, df = 40, see Supplemental Table 1 column (b)) beyond the influence of artifact correction (beta = 4.64, p = 0.006). However, this relationship was not significant any more after controlling for mean heart rate (beta = -1.20 ± 0.66, p = 0.08, see Supplemental Table 1 column (c); trait anxiety score and mean heart rate across participants were moderately correlated: r = 0.39, p = 0.01)), as mean heart rate was also accounting for a significant decrease in HRV (beta = -1.44 ± 0.53, p = 0.01).

HRV and BOLD activity during self-control. To investigate whether HRV could serve as a biomarker of changes in the brain's decision circuitry in the food self-

control paradigm, we analyzed blood oxygenation level-dependent (BOLD) activity measured during the choice task. Our primary general linear model (GLM-CH) tested for regions that correlated with HRV during self-control challenges (CH).

Drawing on earlier work, we presumed that self-control trials should require integrating taste and health values into overall subjective choice values to calculate which option to choose. As self-control positively correlated with HRV, we hypothesized that we should see increased activity in regions known to be involved in the value integration process, the vmPFC and dlPFC. We therefore specifically tested our hypothesis in an anatomical vmPFC mask based on the Harvard-Oxford Cortical Atlas (Desikan et al., 2006). This mask comprised the bilateral ventromedial prefrontal cortex that is part of the brain's valuation system (Bartra et al., 2013; Clithero and Rangel, 2014) and has been shown to integrate taste and health values in the dietary self-control paradigm (Hare et al., 2009; Hare et al., 2011a; Hare et al., 2014; Foerde et al., 2015; Maier et al., 2015).

We indeed found increased BOLD activity in the vmPFC as a function of baseline HRV in Challenge > No Challenge trials (MNI peak: [1 46 0] in the paracingulate / cingulate gyrus, and a small cluster in the cingulate gyrus around [21 41 9], $p < 0.025$, small volume corrected; see Figure 3a). Exploratory whole-brain analyses yielded no other regions that survived correcting for multiple comparisons. The left dlPFC has been presumed to modulate activity in the vmPFC during dietary self-control choices (Hare et al. 2009, 2011). As this might be one potential region linking HRV and self-control, we also tested our hypothesis about a correlation of HRV with BOLD activity in an anatomical mask of the left dlPFC based on the Harvard-Oxford Cortical Atlas. However, we found no BOLD activity in the left dlPFC for the Challenge > No Challenge trials that survived small-volume correction within the anatomical region of left dlPFC.

To establish that activity in the vmPFC region was relevant to the participants' choices, we tested whether the chosen food values were represented in the functional ROI correlating with HRV. An integrated value of the chosen food was calculated in a separate GLM (GLM-SV) and we extracted the betas for this chosen food value in the vmPFC ROI. We found that it encoded the integrated value of the chosen food (mean beta = 0.02 ± 0.005, one-sample t-test $p < 0.001$, $T = 3.52$, $df = 46$).

To investigate the nature of the interaction between HRV and the relative taste and health difference that we observed in our behavioral model, we calculated Pearson correlations between HRV and relative taste and health representations in the vmPFC ROI over all participants. The strength of health and taste difference representations was derived from GLM-HT that examined the impact of health, taste, and recommendations on the BOLD signal. In the vmPFC ROI, HRV was significantly negatively correlated with the relative taste value representation (Pearson r = -0.42, p = 0.002, CI = [-0.60, -0.19]; see Figure 3b), but not with the relative health value (r = - 0.12, p = 0.42, CI = [-0.43,0.21]). Excluding the HRV outlier did not change the result (taste r = -0.43, p = 0.004, CI = [-0.63, -0.17]; health r = -0.09, p = 0.56, CI = [-0.43, 0.23]).

Discussion

We found that higher HRV was associated with better self-control in the face of dietary self-control challenges. More specifically, our results show that the choices of individuals with higher HRV were less affected by tempting taste attributes than choices of participants with lower HRV. In parallel, at the neural level, higher HRV correlated with a decreased representation of taste attributes in vmPFC, a brain region that has been associated with both regulating autonomic responses (Benarroch, 1993) and calculating subjective values of choice options (Bartra et al., 2013; Clithero and Rangel, 2014). Heart rate variability is a measure of physiological fitness that relates to the integrated functioning of the nervous and cardiac systems. Similarly, successful self-control relies on the integration, and potentially modified evaluation, of actions in the context of higher order goal attainment. Our data indicate a significant association between these integration processes at the basic physiological (HRV) and cognitive (SC) levels, suggesting that HRV measures may serve as a useful and easily obtainable biomarker for self-control abilities.

Resting HRV measured over only a few minutes with relatively inexpensive and commercially available equipment predicted subsequent self-control in a dietary choice task as well as a validated psychometric index of dietary behavior (restrained eating scale of the Three Factor Eating Questionnaire, RSE).

Furthermore, as a physiological measure that is presumably outside the domain of conscious control, HRV also has the advantage of being immune to socially desirable reporting (Logan et al., 2008; DeVylder and Hilimire, 2015) or memory errors that can affect the accuracy of self-reports. However, when entered into a joint model, both HRV and RSE were significantly related to dietary self-control suggesting that they explained separate components of the variance in food choice. Thus, it would be useful to combine biomarkers such as HRV with self-report measures like the RSE to give more accurate estimates of future self-control behavior.

The association between HRV and self-controlled behavior is robust to acute changes in environmental context. We previously showed that experiencing an acute stressor resulted in diminished self-control in the 45 minute period following stressor onset (Maier et al., 2015). In this same sample, we find that HRV measured at rest before stressor onset predicts the level of self-control following stress as well as it predicts choice in the control (i.e. not stressed) participants. Behavioral models revealed that individuals with a higher HRV down-regulated taste information in a way that promoted self-control. This was paralleled by our fMRI results: the higher the HRV of the individuals, the lower they represented taste aspects in the vmPFC during self-control challenges. This finding is consistent with the large body of literature implicating the vmPFC in valuation processes during goal-directed choice (see the meta-analyses by Bartra et al. (2013) and Clithero & Rangel (2013)).

As mentioned earlier, methodological standards for HRV measurement and interpretation are still under development. Therefore we need to cautiously interpret our findings and try to rule out the influence of known confounds that could have biased the HRV recording. Our robustness checks show that the number of corrected artifacts and mean heart rate had no effect on the results when we statistically control for both nuisance factors in our regression model.

Another potential limitation is the lack of breathing data. One concern in the psychophysiology literature is an effect of different breathing frequency during the HRV recording that could increase HRV in the recorded baseline. However, as these breathing patterns would occur rather randomly in the population and across recordings, they are rather unlikely to produce meaningfully structured

variance that would help us explain variance in our behavioral and brain models – yet we find a clear relationship between SDNN and our behavioral and brain data. The HRV values we observed lie above the ranges given in the Task Force guidelines (Camm et al., 1996) and Nunan, Sandercock & Brodie (2010). Comparisons to standard values in the literature are difficult to interpret, however. Almost no common standards exist, partially due to the fact that HRV values may depend on measurement factors such as recording length, age of the individuals, artifact correction, etc., that vary between studies and also preclude a direct comparison of our 3-minute recording in healthy young men to values for a 5-minute sample in a middle-aged population. Internally, results from our sample were consistent and there was no indication of outliers driving the effects. Apart from breathing, a wide range of potential confounds was actively controlled by our inclusion / exclusion criteria.

To assess the external validity of our HRV measure, we turned to trait characteristics that have earlier been reported as being related to HRV and found these to also hold in our sample. HRV was inversely related to average heart rate and age, as expected from the literature (Tsuji et al., 1996). Corroborating earlier findings, HRV also was lower individuals with higher trait anxiety (Gaburro et al., 2011; Verkuil et al., 2014).

Linking the association between HRV and self-regulation to a potential underlying neural network has proven difficult in the past. It is unclear how to use tools such as functional MRI to directly test for a general integration of central regulation of autonomic function (as described in Benarroch's Central Autonomic Network, CAN) and cognitive control functions (as postulated by the neurovisceral integration hypothesis). These theories do not make directly falsifiable predictions about neural activity. While the CAN comprises a wide array of cortical and subcortical brain structures, only a subset of these structures might be actively involved in various types of self-regulation, and additionally, observed networks in emotion regulation may differ for explicit and implicit regulation, and again for the correlates of emotional reactivity (Etkin et al., 2015).

Although theories of the neurophysiological basis of HRV do not readily lend themselves to direct testing, previous work has associated HRV with neural activity during affective and cognitive tasks. In a study using Positron Emission

Tomography and an active emotion regulation task, Lane et al. (2009) linked regional cerebral blood flow in the right dorsolateral prefrontal cortex (BA 8, 9, 46), parietal cortex (BA 40), and the left rostral ACC (BA 24,32) with high-frequent (parasympathetic) components of HRV, analyzing 1-minute blocks during which participants immersed themselves into positive, negative, and neutral emotions (evoked by film clips and vignettes of personal emotional memories) while parallel PET and HRV were recorded. Similarly, Gianaros et al. (2004) were able to relate HRV specifically to changes in rCBF in medial orbitofrontal cortex (mOFC), Insula and ACC, Amygdala, Hippocampus and Cerebellum as a function of task demand in working memory tasks. Nugent, Bain, Thayer, Sollers & Drevets (2011) identified rCBF in lateral and medial OFC during a handgrip task that required matching different levels of maximum strength as also being associated with HRV.

In contrast, we examined self-regulation during goal-directed choices rather than emotion regulation or working memory and measured sedentary, resting HRV before the task began rather than HRV during task performance. As mentioned previously, we found a significant relationship between pre-task HRV and taste attribute representations in vmPFC at the time of choice. Contrary to our *a priori* predictions, we did not observe any significant correlations with HRV in the dlPFC during food choices like those reported by Lane and colleagues' in their emotion regulation task. However, the differences in HRV indices and measurement times (resting vs. task) preclude any direct comparisons between the emotion regulation and dietary self-control results. It is possible that HRV measures collected during task performance might be more closely linked to active regulation processes in dlPFC. However, our goal in the current study was to test whether simple, task-independent measures of HRV are associated with dietary self-control. What does appear to be consistent is that individual differences in HRV are correlated with activity in neural regions linked to task performance across several domains (e.g. emotion regulation, working memory, physical effort, and dietary self-control). Together these results indicate that future efforts to link cognition with both central and peripheral neurophysiology may promote a better understanding of the nature of individual differences in health and behavior as well as providing opportunities for prediction and early intervention against potential dysfunctions.

One limitation of the current work and its interpretations is that we do not yet understand precisely how metabolic and endocrine processes relate to self-control or whether and how they processes lead to higher or lower HRV. However, our study presents an important initial step in linking total HRV to self-control ability. This result suggests total HRV should be considered when investigating links between self-control and allostatic capacity in addition to more direct indices of vagally mediated HRV such as RMSSD and high-frequency HRV. Further progress could be made by addressing this question with causal manipulations, for example by inducing endocrine signals of hunger and satiety and investigating whether the association between total HRV and self-control success varies during these states. Another interesting avenue to pursue is whether plasticity-induced changes that enable better regulation, for example through transcranial electrical stimulation or magnetic stimulation of the dlPFC, might also lead to an increase in HRV. A study in autistic children suggests this might be the case: Wang et al. (2015) found that weekly treatment with low-frequency repetitive transcranial magnetic stimulation (rTMS) for 3 months improved both chronic autonomic imbalance (i.e., higher low frequency and lower high-frequency contributions to total HRV, putatively reflecting a tonically high arousal level due to activation of the sympathetic nervous system) and tonically elevated skin conductance levels that are commonly seen in autism. This change was accompanied by decreased irritability, hyperactivity, and less stereotyped and compulsive behavior in the autistic children. Future work should therefore address this regulatory mechanism in a healthy population with a similar causal manipulation by stimulation techniques to further explore the nature of the link between neural correlates of self-regulation and physiological markers of allostatic capacity.

Conclusion

Heart rate variability is a marker associated with cardiovascular and mental health that has previously been associated with improved self-regulation in the domain of emotion. Our results indicate that heart rate variability also explains variation in self-control success in dietary choice on the same order of magnitude as an established psychometric index of restrained eating. Both HRV and the psychometric restrained eating scale contributed independently to explaining

variance in our behavioral model of self-control and could be used in combination to better predict dietary self-control levels.

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Tables

Table 1. Predictors of self-control failure.

Fixed effects	(a) Basic Model (BM)	(b) BM without outlier	(c) BM controlling corrected artifacts and mean heart rate
Intercept	0.0133	-0.008	0.3316
	(0.2725)	(0.2807)	(1.2031)
Stress (S)	-0.1005	-0.0647	-0.0621
	(0.3703)	(0.3765)	(0.3811)
HRV	-0.0215	-0.081	-0.1297
	(0.2752)	(0.3055)	(0.3227)
Hdiff	-1.0997 ****	-1.061 ****	-1.0995 ****
	(0.0818)	(0.0815)	(0.0818)
Tdiff	0.4604 ****	0.4624 ****	0.4604 ****
	(0.0661)	(0.0669)	(0.0661)
REC	-0.6443 ****	-0.6362 ****	-0.6443 ****
	(0.0624)	(0.0633)	(0.0624)
# of Artifacts	--	--	0.0411
			(0.0688)
Mean Heart Rate	--	--	-0.0064
			(0.0188)
RSE	-0.3661 *	-0.3644 *	-0.3201
	(0.1855)	(0.1833)	(0.1995)
Stress x HRV	-0.2465	-0.1644	-0.2036
	(0.3887)	(0.3956)	(0.3931)
Stress x Hdiff	0.1367	0.1078	0.1360
	(0.1069)	(0.1068)	(0.1069)
Stress x Tdiff	0.3168 ***	0.319 ***	0.3167 ***
	(0.0909)	(0.0915)	(0.0909)
Stress x REC	-0.0177	-0.0203	-0.0179
	(0.0853)	(0.0863)	(0.0853)
HRV x Hdiff	-0.2375 **	-0.1602	-0.2382 **
	(0.0894)	(0.0896)	(0.0894)
HRV x Tdiff	-0.1991 **	-0.226 **	-0.1993 **
	(0.0708)	(0.0729)	(0.0708)
HRV x REC	0.0230	0.0549	0.0227
	(0.0652)	(0.0706)	(0.0653)
S x HRV x Hdiff	0.0787	0.0154	0.0789
	(0.1167)	(0.1127)	(0.1168)
S x HRV x Tdiff	0.1391	0.1712	0.1391
	(0.1014)	(0.0985)	(0.1014)
S x HRV x REC	-0.1122	-0.1361	-0.1118
	(0.0922)	(0.0922)	(0.0922)

All estimates are reported with their Standard Error of the Mean (SEM) in brackets. Stars denote the significance level:

**** = $p < 0.0001$
*** = $p < 0.001$
** = $p < 0.01$
* = $p < 0.05$

(a) Results from a generalized linear mixed model fit by maximum likelihood (Laplace approximation). Self-control failure was modeled by a binomial regressor that represented choosing the tastier, less healthy item in trials in which health and taste were not aligned (challenge trials). The model contained participant-level variables for stress and the HRV baseline and trial-level variables for the absolute difference in health (Hdiff), taste (Tdiff), and the health recommendations (REC). An additional regressor controlled for effects of the restrained eating trait score measured by the Three Factor Eating Questionnaire (RSE) in order to assess the performance of HRV in predicting self-control beyond a validated psychometric scale of restrained eating.

(b) Results for the model depicted in column a), excluding all data of the HRV outlier.

(c) In order to control for the effect of artifact correction and baseline heart rate, we augmented the model from column a) by adding regressors containing the number of corrected artifacts and the mean heart rate (after deletion of artifacts) in the dataset. Predictions for the significant effects did not qualitatively change compared to the basic model depicted in column a), and number of corrected artifacts and mean heart rate did not predict self-control performance.

Figures

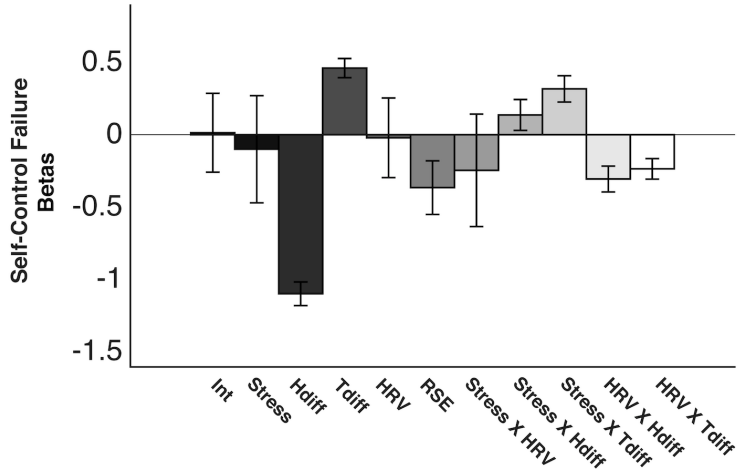


Figure 1. Self-control model. While greater taste differences (Tdiff) increased self-control failure, higher resting HRV was associated with a decreased influence of taste attributes on choices that required self-control. Similarly, it was associated with an increased influence of health attributes (Hdiff) that reduced self-control failures. Both HRV and the expression of a restrained eating trait (RSE) predicted independent and significant portions of the variation in self-control behavior.

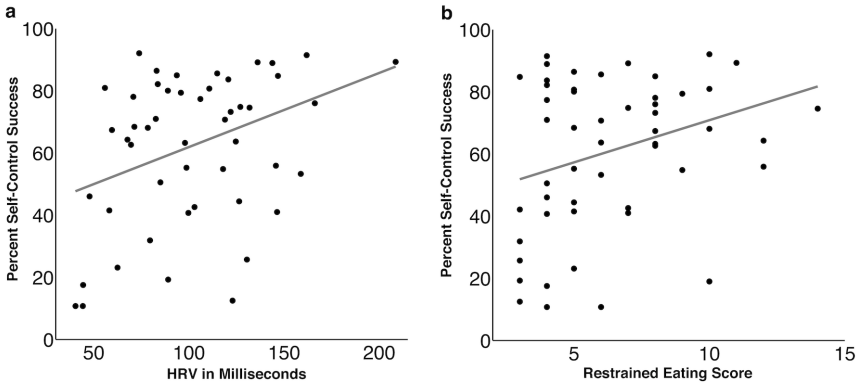


Figure 2. Correlates of dietary self-control success. The comparison of both panels shows that both total resting HRV, measured as SDNN in milliseconds **(a)** and restrained eating score **(b)** correlated to a fair degree with dietary self-control success.

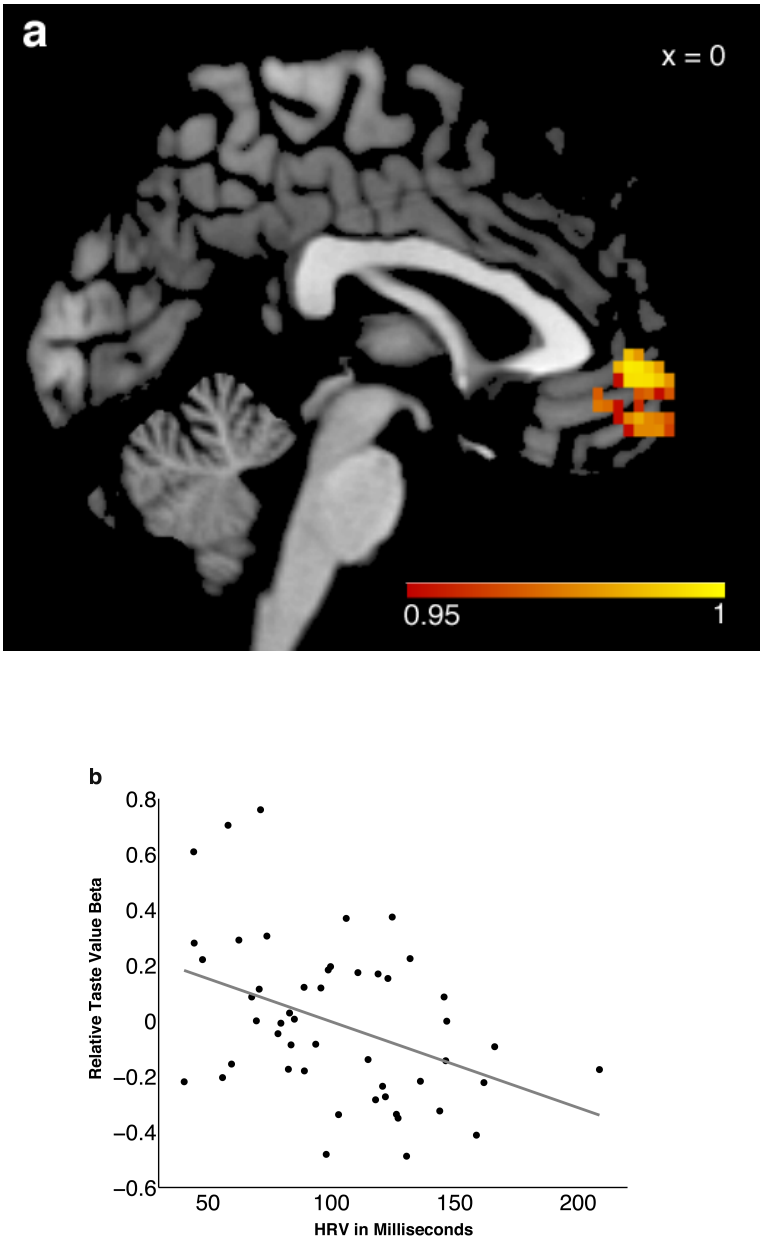
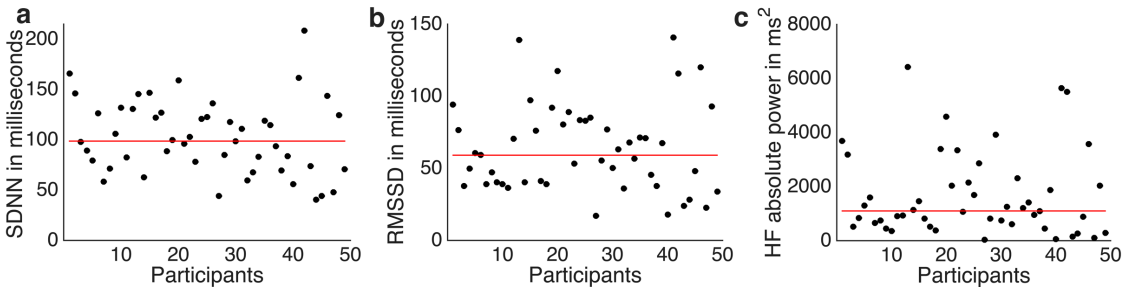


Figure 3. Brain correlates of HRV. Panel **(a)**: Baseline HRV positively correlated with higher activity in Self-Control Challenge > No Challenge trials in the ventromedial prefrontal cortex ($p < 0.025$, small-volume corrected). Within this vmPFC ROI, the relative taste representation (taste of the chosen minus taste of the non-chosen food) correlated negatively with individual HRV, as depicted in panel **(b)**.

Supplemental Material for Study 3.

Supplemental Figures

Figure 1. Heart Rate Variability (HRV) indices



The panels depict the raw values for each participant's **(a)** SDNN, **(b)** RMSSD, and **(c)** HF absolute power measure of HRV. The red line in each plot indicates the Median value.

Supplemental Methods

HRV. In addition to the *time domain* measures discussed in the main text, the representation in the *frequency domain* allows to putatively classify the sources of fluctuations, as underlying processes live on different time scales: High frequency (HF) variability is caused by factors that fluctuate on the order of milliseconds and most likely represents parasympathetic contributions. Variance in the HF band is often reflecting the phenomenon that the pace of the heartbeat varies with breathing frequency ("Respiratory Sinus Arrhythmia", RSA), which is therefore sometimes also called respiratory frequency band (Berntson et al., 1997). Low Frequency (LF) variability depends on fluctuations that live on the order of seconds and putatively reflects primarily sympathetic contributions, Very Low Frequencies (VLF) reflect adaptation of HRV on several occasions during the day (e.g., during changes in thermoregulation), and changes in Ultra-Low Frequencies (ULF) might reflect for example diurnal hormonal rhythms (Berntson et al., 1997).
For comparison purposes with earlier reports, we also evaluated the root mean square of successive differences in RR intervals (RMSSD) in the time domain that putatively (yet not exclusively, (Berntson et al., 2005)) reflects the short-term

fluctuations in HRV. As RMSSD and high and low frequency estimates were reported to depend heavily on the artifact correction method, and deletion had been demonstrated to perform worse than interpolation in maintaining the true underlying signal for all measures except SDNN (Salo et al., 2001), preprocessing was then repeated with the same setup as for SDNN, but the identified artifacts were replaced by linear interpolation (i.e., replacing the artifact by fitting a straight line between the adjacent RR intervals) in order to calculate RMSSD and frequency-domain measures of HRV following the recommendations in Salo et al. (2001).

RMSSD was calculated as

(3)

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N-1}\left(RR_{j+1} - RR_j\right)^2}$$

Frequency-domain measures of HRV were also calculated with the Artiifact software suite, using Fast Fourier Transforms (Berntson and Stowell, 1998; Kaufmann et al., 2011) with an interpolation rate of 4 Hz (spline interpolation) and a Hanning window width that matched the total length of the edited recording (max. 180 seconds or slightly less in case of deletion correction). Frequency bands were bounded between 0.003 and 0.04 Hz for the very low frequency band, 0.04 and 0.15 Hz for the low frequency band, and 0.15 and 0.4 Hz for the high frequency band.

Supplemental Results

HRV. The median RMSSD at 59.1 ± 24.66 ms did not differ between the participants who would later enter the Stress and Control treatments (S: 50.4 ± 22.4 ms, C: 64 ± 27 ms; p = 0.48, Z = - 0.71, Wilcoxon rank sum test).

We also calculated frequency domain measures, but due to the short recording only evaluate the high frequency band that can be reliably sampled in recordings longer than 1 minute. We had chosen a 3-minute baseline recording to match the length of our stress induction period. As this is slightly shorter than the 5-minute span that is usually collected for comparison across studies (although

even a minimum duration of 1 minute is sufficient to record the high-frequency band according to Camm et al. (1996) and 2-minute recordings already reach almost perfect agreement with the gold standard 4-5 minute measurements for SDNN and RMSSD according to Munoz et al. (2015), we cannot observe at least 10 complete cycles of the low frequency band that are given as a heuristic for the minimal recording length with regard to getting a good-enough resolution in lower frequency ranges (Camm et al., 1996; Berntson et al., 1997). The lower frequency band at the lower end of its bandwidth has a period of 25 seconds (0.04 Hertz), and would thus require at least 10 x 25 seconds for 10 complete cycles and thus might be undersampled in our recording. Neither would our recording capture the very low frequency band reliably. We therefore refrain from interpreting the values obtained in these frequency ranges, but report them for completeness. We restrict interpretation and modeling to the total HRV (SDNN) and the high-frequency power spectrum that is mainly influenced by the effects of respiratory sinus arrhythmia, which in turn is linearly related to cardiac vagal control (Katona and Jih, 1975).

In the high frequency (HF) range, we observed a median absolute HF value of 1100.6 ± 1212.4 ms^2 (indifferent between S and C groups: Median S = 935.8 ± 864.6 ms2, C = 1246.3 ± 1543.4 ms2; p = 0.43, Z = -0.79). As the distribution of the HF measure is highly skewed, we also report normalized values that were obtained by applying a natural logarithm transformation. The median HF log value was 7 ± 0.86 MAD.

For completeness, we report the low (LF) and very low frequency (VLF) band, although these are most likely not reliably sampled in such a short recording and will thus not be further interpreted. In the LF band, the Median of the absolute values was 2526.6 ± 2454.4 ms^2 (log values: 7.8 ± 0.7), and 3902.1 ± 4383.2 ms^2 in the VLF band (log: 8.3 ± 1).

As expected from earlier descriptions in the literature (Kleiger et al., 1991; Camm et al., 1996; Massin et al., 1999; Kupper et al., 2004; Wang et al., 2005), we found SDNN to be strongly correlated with RMSSD ($r = 0.79$, $p < 0.001$) and the absolute values in the HF power spectrum ($r = 0.71$, $p < 0.001$). RMSSD was also strongly correlated with the absolute values of the HF power band ($r = 0.91$, $p < 0.001$).

As a robustness check, we tried to predict SDNN from potentially influential factors based on previous reports in the literature (Tsuji et al., 1996; Antelmi et al., 2004; Heathers, 2014). We ran a general linear model (GLM-HRV, see Supplemental Table 1) with regressors representing the mean heart rate, number of corrected artifacts, BMI, age, total exercise per week, systolic and diastolic blood pressure for each participant. Among these factors, only the mean heart rate (beta = -1.65 ± 0.52, p = 0.003, df = 41) and the number of corrected artifacts significantly predicted SDNN (beta = 4.92 ± 1.48, p = 0.002).

Paralleling the robustness check we used for SDNN, we ran a general linear model (GLM-HRV) with regressors representing the mean heart rate, number of corrected artifacts, BMI, age, total exercise per week, systolic and diastolic blood pressure for each participant to predict RMSSD. We obtained similar results as for SDNN, with significant predictors for mean heart rate (beta = -2.04, p< 0.001) and artifact correction (beta = 4.44, p < 0.001, df = 41). The same was true for absolute value in the HF band (beta mean heart rate = -85.25, p = 0.0002; beta artifact correction = 158.51, p = 0.01, df = 41).

Self-control behavior. For RMSSD, we observed a slightly weaker, insignificant relationship with self-control success (r = 0.21, p = 0.16). The same was true for the HF absolute values (r = 0.15, p = 0.32; Stress: r = 0.15, p = 0.32, Controls: r = 0.17, p = 0.46).

In our behavioral model of self-control, higher total HRV (SDNN) was associated with a decreased influence of taste attributes in self-control challenges, in which health and taste attributes were not aligned. We obtained qualitatively similar, yet insignificant effects for the indices of short-term heart rate variability RMSSD (see supplemental Table 2) and HF absolute power (HF abs, see supplemental Table 3) when we replaced higher total HRV (SDNN) with these measures. Higher HRV was qualitatively associated with a decreased influence of taste attributes in self-control challenges, in which health and taste attributes were not aligned.

fMRI. Paralleling our behavioral results, the relationship between higher HRV and higher BOLD activity during challenge trials compared to non-challenging trials in

vmPFC held for the total HRV as indexed by SDNN, but was not significant for the RMSSD and HF absolute power measures. Focusing exclusively on the RMSSD and HF power band as indices of phasic vagal control may thus not be a useful strategy for assessing correlates of self-control in our goal-directed dietary choice paradigm. The SDNN measure may incorporate further information that adds robustness the statistical relationship between HRV and self-regulation. It likely contains an estimate of phasic vagal cardiac regulation that can still be regarded in our short sampling period as having sufficiently good resolution, while the information on other fluctuations in the metabolism that might be relevant to self-control is captured in a less precise manner. Nevertheless, when controlling for known influences on HRV, it seems that this additional information that might index metabolic and endocrine processes in the organism among others adds some power to our self-control index.

Supplemental Tables

Table 1. General linear model predicting SDNN (GLM-HRV).

Regressor	(a) Basic Model (BM)	(b) BM controlling for trait anxiety level	(c) BM controlling for trait anxiety level and mean heart rate
Intercept	154.25	140.25	196
	(83.65)	(89.5)	(85.62)
# of Artifacts	4.92 **	4.64 **	4.63 **
	(1.48)	(1.59)	(1.47)
Mean Heart Rate	-1.65 **	--	-1.44 **
	(0.52)		(0.53)
Trait Anxiety	--	-1.62 *	-1.2
		(0.70)	(0.66)
Age	-3.12	-4.51	-4.82
	(2.37)	(2.71)	(2.52)
BMI	1.78	2.84	2.59
	(2.71)	(2.91)	(2.71)
Sport per week	-1.68	0.43	-2.9
	(2.74)	(2.74)	(2.83)
Systole	0.39	0.17	0.43
	(0.42)	(0.44)	(0.42)
Diastole	0.37	0.23	0.43
	(0.56)	(0.59)	(0.56)

All estimates are reported their Standard Error of the Mean (SEM) in brackets.
Stars denote the significance level:

** = $p < 0.01$
* = $p < 0.05$

(a) Results from a generalized linear model with possible determinants of HRV (represented as untransformed values of SDNN in milliseconds): the number of artifacts corrected in the dataset, mean heart rate (after artifact correction by deletion), age, body mass index (BMI), total number of times per week that participants exercised either for cardio performance or building strength, systolic and diastolic blood pressure.

(b) In the model depicted in column a), we replaced the regressor for the mean heart rate with the trait anxiety score as measured by the Spielberger State-Trait-Anxiety Inventory.

(c) In order to assess whether trait anxiety explains additional variance beyond an increase in mean heart rate, we augmented the model from column a) by adding the regressor with the trait anxiety score, so that mean heart rate and trait anxiety competed for variance in the same model. When doing so, mean heart rate remained significant as a predictor of HRV, but trait anxiety did not explain further variance.

Table 2. Model assessing the influence of RMSSD on self-control failure controlling for the effect of a restrained eating trait.

Fixed effects	Estimate	SEM	z	p
Intercept	0.3477	1.6838	0.206	0.8364
Stress (S)	- 0.1199	0.3985	-0.301	0.7633
RMSSD	-0.2547	0.3719	-0.685	0.4934
Hdiff	-1.0479	0.0783	-13.375	< 2e-16
Tdiff	0.4700	0.0656	7.169	7.54e-13
REC	-0.6445	0.0622	-10.368	< 2e-16
# of Artifacts	0.0067	0.0827	0.081	0.9358
Mean heart rate	-0.0053	0.0268	-0.199	0.8422
RSE	-0.4267	0.1963	-2.174	0.0297
Stress x RMSSD	-0.0515	0.4126	-0.125	0.9008
Stress x Hdiff	0.0769	0.1043	0.738	0.4605
Stress x Tdiff	0.3195	0.0911	3.506	0.0005
Stress x REC	-0.0180	0.0852	-0.211	0.8326
RMSSD x Hdiff	-0.0140	0.0733	-0.191	0.8482
RMSSD x Tdiff	-0.0859	0.0579	-1.484	0.1378
RMSSD x REC	0.0729	0.0575	1.267	0.2052
S x RMSSD x Hdiff	-0.0772	0.1096	-0.705	0.4809
S x RMSSD x Tdiff	0.1470	0.0952	1.544	0.1225
S x RMSSD x REC	-0.0225	0.0886	-0.254	0.7994

Results from a generalized linear mixed model fit by maximum likelihood (Laplace approximation). Self-control failure was modeled by a binomial regressor that represented choosing the tastier, less healthy item in trials in which health and taste were not aligned (challenge trials). The model contained subject-level variables for stress and the RMSSD baseline value and all possible interactions with the regressors for the absolute difference in health (Hdiff), taste (Tdiff), and the health recommendations. The model controlled for effects of the restrained eating trait score measured by the Three Factor Eating Questionnaire (RSE). RSE explained additional variance in self-control performance. Analogously to the model for SDNN, we included nuisance regressors to control for the number of corrected artifacts and the mean heart rate (after deletion of artifacts) in the dataset. All estimates are reported with their standard error of the mean (SEM).

Table 3. Model assessing the influence of ln HF absolute power (ln HF) on self-control failure controlling for the effect of a restrained eating trait.

Fixed effects	Estimate	SEM	z	p
Intercept	1.5632	1.7076	0.915	0.3600
Stress (S)	-0.3854	2.6826	-0.144	0.8858
Ln HF	-0.0629	0.2520	-0.250	0.8029
Hdiff	-0.8593	0.3750	-2.291	0.0219
Tdiff	0.8513	0.3382	2.517	0.0118
REC	-0.7378	0.3232	-2.283	0.0224
# of Artifacts	-0.0364	0.0688	-0.529	0.5970
Mean heart rate	0.1376	0.2460	0.559	0.5759
RSE	-0.1617	0.0716	-2.259	0.0239
Stress x ln HF	0.0349	0.3812	0.092	0.9270
Stress x Hdiff	-0.8854	0.7295	-1.214	0.2248
Stress x Tdiff	-0.6043	0.6480	-0.932	0.3511
Stress x REC	-0.0934	0.6051	-0.154	0.8774
Ln HF x Hdiff	-0.0279	0.0539	-0.517	0.6049
Ln HF x Tdiff	-0.0568	0.0477	-1.191	0.2337
Ln HF x REC	0.0142	0.0458	0.311	0.7561
S x ln HF x Hdiff	0.1393	0.1038	1.341	0.1798
S x ln HF x Tdiff	0.1354	0.0934	1.450	0.1472
S x ln HF x REC	0.0096	0.0862	0.111	0.9113

Results from a generalized linear mixed model fit by maximum likelihood (Laplace approximation). Self-control failure was modeled by a binomial regressor that represented choosing the tastier, less healthy item in trials in which health and taste were not aligned (challenge trials). The model contained subject-level variables for stress and the ln HF baseline value and all possible interactions with the regressors for the absolute difference in health (Hdiff), taste (Tdiff), and the health recommendations. The model controlled for effects of the restrained eating trait score measured by the Three Factor Eating Questionnaire (RSE). RSE explained additional variance in self-control performance. Analogously to the model for SDNN, we included nuisance regressors to control for the number of corrected artifacts and the mean heart rate (after deletion of artifacts) in the dataset. All estimates are reported with their standard error of the mean (SEM).

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